

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 May 2003 (01.05.2003)

PCT

(10) International Publication Number
WO 03/035066 A1

(51) International Patent Classification⁷: **A61K 31/422**,
A61P 43/00, C07D 413/04, 413/14, 521/00

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(21) International Application Number: PCT/GB02/04754

(22) International Filing Date: 22 October 2002 (22.10.2002)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0125365.7 23 October 2001 (23.10.2001) GB
0205372.6 7 March 2002 (07.03.2002) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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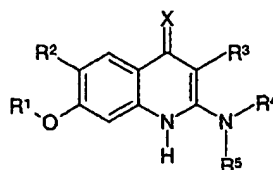
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 2-AMINOQUINOLONE DERIVATIVES FOR USE AS IMPDH INHIBITORS



(1)

(57) Abstract: Quinolone derivatives of formula (1) are described; wherein: X is an O or S atom; R¹ is an aliphatic, cycloaliphatic, or cycloalkyl-alkyl-group; R² is a -CN group or an optionally substituted heteroaromatic group; R³ is a hydrogen atom or an alkyl, -CN, -CO₂H, -CO₂R⁶ or -CONR⁷R⁸ group; R⁴ is a chain -Alk¹-L¹-Alk²-R⁹; R⁵ is a hydrogen atom or an alkyl group; or NR⁴R⁵ forms an optionally substituted heterocycloaliphatic ring optionally fused to an optionally substituted monocyclic C₆₋₁₂ aromatic group or an optionally substituted heterocyclic C₁₋₉ heteroaromatic group; and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof. The compounds are potent inhibitors of IMPDH and are of use as immunosuppressants, anti-cancer agents, anti-inflammatory agents, antipsoriatic and anti-viral agents.

2-AMINOQUINOLONE DERIVATIVES FOR USE AS IMPDH INHIBITORS

This invention relates to a series of quinolones, to processes for their preparation, to pharmaceutical compositions containing them and to their use
5 in medicine.

Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the *de novo* synthesis of guanine nucleotides. IMPDH catalyses the β -nicotinamide adenine dinucleotide (NAD)-dependant oxidation
10 of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) (Jackson R.C. et al., Nature, 256, pp. 331-333, (1975)). Guanine nucleotides are essential to the cell for RNA and DNA synthesis, intermediates in signalling pathways and as energy sources for metabolic pathways.

15 IMPDH is ubiquitous in eukaryotes, bacteria and protozoa (Y. Natsumeda & S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93, (1993)). Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced (F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et al J. Biol. Chem., 265, pp 5292-5295, (1990)). Each is 514
20 amino acids and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa (Y. Yamada et. al., Biochemistry, 27, pp. 2737-2745, (1988)). It is thought that type I is the predominant isoform expressed in normal cells, whilst type II is upregulated in neoplastic and replicating cells. Studies have
25 postulated that selective inhibition of type II IMPDH could provide a therapeutic advantage by reducing potential toxicity effects caused by inhibiting the type I isoform (Pankiewicz K.W, Expert Opin. Ther. Patents 11 (7) pp 1161-1170, (2001)).

30 The *de novo* synthesis of guanine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the *de novo*, rather than the salvage pathway to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen

(A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison et. al., Ciba Found. Symp., 48, 207, (1977)). Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

5

Mycophenolic acid (MPA) and some of its derivatives have been described in United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 as potent, uncompetitive, reversible inhibitors of human IMPDH type I ($K_i = 33$ nM) and type II ($K_i = 9$ nM). MPA has been
10 demonstrated to block the response of B and T-cells to mitogen or antigen (A.C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993)).

Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. (R.E. Morris, Kidney Intl., 49,
15 Suppl. 53, S-26, (1996)). However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*,
20 was recently approved to prevent acute allograft rejection following kidney transplantation (i.e. renal allograft failure) and heart transplantation. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H.W. Sollinger, Transplantation, 60, pp. 225-232, (1995); J. Kobashigawa Transplant, 66, pp. 507, (1998)). Mycophenolate mofetil has also been used
25 for the treatment of rheumatoid arthritis. The experimental use of mycophenolate mofetil in the treatment of systemic lupus erythematosus, lupus nephritis, myasthenia gravis, inflammatory eye disease, autoimmune and inflammatory skin disorders (including psoriasis) and glomerular disease has also been described (R. Bentley, Chem. Rev., 100, pp. 3801-3825,
30 (2000)). Mycophenolate mofetil has also been postulated to be of use for the treatment of atopic dermatitis (Grundmann-Kollman M *et al*, Archives of Dermatology, 137 (7), pp. 870-873, (2001)) and has been shown to be effective in predictive animal models of multiple sclerosis (Tran G.T *et al*, International Immunopharmacology, 1 (9-10) pp. 1709-1723, (2001)).

Several clinical observations, however, limit the therapeutic potential of this drug. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

5 Nucleoside analogues such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH (L. Hedstrom, et. al., Biochemistry, 29, pp. 849-854, (1990)). These nucleoside analogues are competitive inhibitors of IMPDH, but also inhibit other NAD dependant enzymes. This lack of specificity limits the therapeutic application of these compounds. New agents with improved selectivity for
10 IMPDH would represent a significant improvement over these nucleoside analogues. Mizoribine (Bredinin®) has been approved in Japan for multiple indications in transplantation and autoimmune diseases including prevention of rejection after renal transplantation, idiopathic glomerulonephritis, lupus nephritis and rheumatoid arthritis.

15

Vertex has recently disclosed a series of novel IMPDH inhibitors (WO 97/40028), of which VX-497 has been evaluated for the treatment of psoriasis.

It is also known that IMPDH plays a role in other metabolic events. Increased
20 IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumour cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy (M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991), Pankiewicz K.W., Exp. Opin. Ther. Patents, 11, pp. 1161-1170, (2001)). IMPDH has also been shown to play a role in the
25 proliferation of smooth muscle cells, indicating that inhibitors of IMPDH may be useful in preventing restenosis or other hyperproliferative vascular diseases (C.R. Gregory et. al., Transplantation, 59, pp. 655-61, (1995); PCT publication WO 94/12184; and PCT publication WO 94/ 01105).

30 Additionally, IMPDH has been shown to play a role in viral replication in some virus-infected cell lines. (S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290, (1993)). VX-497 is currently being evaluated for the treatment of hepatitis C in humans.

Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties. Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-inflammatory agents, antipsoriatic and anti-viral agents.

5

Japanese Patent Application number JP04164070 discloses the synthesis of a general class of quinolones for use as bactericides.

10

International Patent Application numbers WO-A-99/55677 and WO-A-00/21949 both disclose a general class of 2-aminoquinolones for use as inhibitors of methionyl t-RNA synthetase and antibacterial agents.

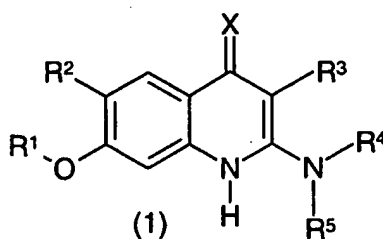
Co-pending International Patent Application number WO-A-01/81340 discloses a general class of heterocycles as inhibitors of IMPDH.

15

The present inventors disclose new potent IMPDH inhibitors based on substituted quinolone derivatives.

Thus according to one aspect of the invention we provide a compound of formula (1):

20



wherein:

X is an O or S atom;

R¹ is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

25

R² is a -CN group or an optionally substituted heteroaromatic group;

R³ is a hydrogen atom or an alkyl, -CN, -CO₂H, -CO₂R⁶ or -CONR⁷R⁸ group, in which R⁶ is an alkyl group and R⁷ and R⁸, which may be the same or different, is each a hydrogen atom or an alkyl group;

R^4 is a chain $-Alk^1-L^1-Alk^2-R^9$ in which Alk^1 is a covalent bond or an optionally substituted aliphatic chain, L^1 is a covalent bond or a linker atom or group, Alk^2 is a covalent bond or a C_{1-3} alkylene chain and R^9 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; provided that R^4 is not a hydrogen atom;

R^5 is a hydrogen atom or an alkyl group;

or NR^4R^5 forms an optionally substituted heterocycloaliphatic ring optionally fused to an optionally substituted monocyclic C_{6-12} aromatic group or an optionally substituted monocyclic C_{1-9} heteroaromatic group;

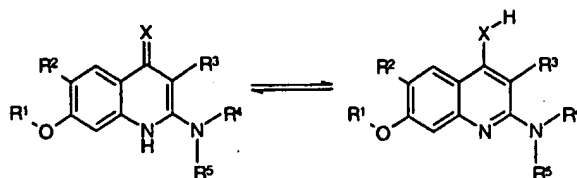
and the salts, solvates, hydrates, tautomers, isomers or *N*-oxides thereof;

provided that the compound of formula (1) is other than:

7-methoxy-2-methylamino-6-oxazol-5-yl-1H-quinolin-4-one or
2-dimethylamino-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one.

15

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (*E* or *Z* isomers). The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$) – enol ($CH=CHOH$) tautomers. Quinolones may also exist as tautomers; one possible example is illustrated below:



Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

It will also be appreciated that where desired the compounds of the invention may be administered in a pharmaceutically acceptable pro-drug form, for example, as a protected carboxylic acid derivative, e.g. as an acceptable ester. It will be further appreciated that the pro-drugs may be converted *in vivo* to the active compounds of formula (1), and the invention is intended to extend to such pro-drugs. Such prodrugs are well known in the literature, see for example International Patent Application No. WO 00/23419, Bodor N. (Alfred Benson Symposium, 1982, 17, 156-177), Singh G. *et al* (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard H. (Design of Prodrugs, 1985, Elsevier, Amsterdam).

In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

The term "aliphatic group" is intended to include optionally substituted straight or branched C₁₋₁₀alkyl, e.g. C₁₋₆ alkyl, C₂₋₁₀alkenyl e.g. C₂₋₆alkenyl or C₂₋₁₀alkynyl e.g. C₂₋₆alkynyl groups. Optional substituents when present on these groups include those optional substituents mentioned hereinafter.

Thus as used herein the term "alkyl", whether present as a group or part of a group includes straight or branched C₁₋₁₀alkyl groups, for example C₁₋₆alkyl groups such as methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl or *t*-butyl groups. Optional substituents when present on these groups include those optional substituents mentioned hereinafter.

The terms "alkenyl" or "alkynyl" are intended to mean straight or branched C₂₋₁₀alkenyl or C₂₋₁₀alkynyl groups such as C₂₋₆alkenyl or C₂₋₆alkynyl groups such as -CHCH₂, -CHCHCH₃, -CH₂CHCHCH₃, -CCH, -CH₂CCH and -CH₂CCCH₃ groups. Such groups may be substituted by those optional substituents mentioned hereinafter.

Particular examples of aliphatic groups include optionally substituted C₁₋₆ alkyl groups such as -CH₃, -CH₂CH₃, -CH(CH₃)₂, -(CH₂)₂CH₃, -(CH₂)₃CH₃, -CH(CH₃)CH₂CH₃, -CH₂CH(CH₃)₂, -CH₂C(CH₃)₃, -C(CH₃)₃, -(CH₂)₄CH₃, -(CH₂)₅CH₃, or C₂₋₆alkenyl or C₂₋₆alkynyl groups such as -CHCH₂,
 5 -CHCHCH₃, -CH₂CHCH₂, -CHCHCH₂CH₃, -CH₂CHCHCH₃, -(CH₂)₂CHCH₂, -CCH, -CCCH₃, -CH₂CCH, -CCCH₂CH₃, -CH₂CCCH₃, or -(CH₂)₂CCH groups.

The term "aliphatic chain" is intended to include those alkyl, alkenyl or alkynyl groups as just described where a terminal hydrogen atom is replaced by a
 10 covalent bond to give a divalent chain.

Examples of aliphatic chains include optionally substituted C₁₋₆ alkylene chains such as -CH₂-, -CH₂CH₂-, -CH(CH₃)CH₂-, -(CH₂)₂CH₂-, -(CH₂)₃CH₂-, -CH(CH₃)(CH₂)₂CH₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂-, -C(CH₃)₂CH₂-,
 15 -CH₂C(CH₃)₂CH₂-, -(CH₂)₂CH(CH₃)CH₂-, -CH(CH₃)CH₂CH₂-, -CH(CH₃)CH₂CH(CH₃)CH₂-, -CH₂CH(CH₃)CH₂CH₂-, -(CH₂)₂C(CH₃)₂CH₂-, -(CH₂)₄CH₂-, -(CH₂)₅CH₂-, or C₂₋₆alkenylene or C₂₋₆alkynylene chains such as -CHCH-, -CHCHCH₂-, -CH₂CHCH-, -CHCHCH₂CH₂-, -CH₂CHCHCH₂-, -(CH₂)₂CHCH-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂-,
 20 -(CH₂)₂CCH- chains. More particular examples include optionally substituted C₁₋₃ alkylene chains selected from -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂-, -C(CH₃)₂- and -CH₂CH(CH₃)- chains.

The term "cycloaliphatic group" includes optionally substituted non-aromatic
 25 cyclic or multicyclic, saturated or partially saturated C₃₋₁₀ ring systems, such as, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, adamantyl, norbornyl, norbornenyl, bicyclo[2.2.1]heptanyl or bicyclo[2.2.1]heptenyl. Particular examples include optionally substituted C₃₋₆
 30 cycloalkyl ring systems such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents present on those groups include those substituents mentioned hereinafter.

The term "cycloalkyl-alkyl- group" refers to a C₁₋₆ alkyl group (as described herein) where a terminal hydrogen atom is replaced by a C₃₋₆ cycloalkyl ring (as described herein). Examples include -(CH₂)₁₋₆-cyclopropyl, -(CH₂)₁₋₆-cyclobutyl, -(CH₂)₁₋₆-cyclopentyl or -(CH₂)₁₋₆-cyclohexyl.

5

The term "heterocycloaliphatic group" refers to an optionally substituted 3 to 10 membered saturated or partially saturated monocyclic or saturated or partially saturated multicyclic hydrocarbon ring system containing one, two, three or four L² linker atoms or groups. Particular examples of suitable L² atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R¹⁰)- [where R¹⁰ is a hydrogen atom or a C₁₋₆ alkyl group], -N(R¹⁰)N(R¹⁰)-, -N(R¹⁰)O-, -ON(R¹⁰)-, -CON(R¹⁰)-, -OC(O)N(R¹⁰)-, -CSN(R¹⁰)-, -N(R¹⁰)CO-, -N(R¹⁰)C(O)O-, -N(R¹⁰)CS-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, -N(R¹⁰)CON(R¹⁰)-, -N(R¹⁰)CSN(R¹⁰)-, or -N(R¹⁰)SO₂N(R¹⁰)- groups. Where the linker group contains two R¹⁰ substituents, these may be the same or different. Optional substituents present on the heterocycloaliphatic groups include those substituents mentioned hereinafter.

Particular examples of heterocycloaliphatic groups include optionally substituted cyclobutanonyl, cyclopentanonyl, cyclohexanonyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, oxazolidinyl, oxazolidinonyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazoliny, e.g. 2-imidazoliny, imidazolidinyl, pyrazoliny, e.g. 2-pyrazoliny, pyrazolidinyl, thiazoliny, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, pyranonyl, piperidinyl, piperidinonyl, quinuclidiny, 1,4-dioxanyl, morpholinyl, morpholinonyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, N-C₁₋₆ alkylpiperazinyl, homopiperazinyl, dihydrofuran-2-onyl, tetrahydropyran-2-onyl, isothiazolidinyl 1,1-dioxide, [1,2]thiazinanyl 1,1-dioxide, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrazolidin-3-onyl, tetrahydrothiopyranyl 1,1-dioxide, tetrahydrothiophenyl 1,1-dioxide, 1,3,5-trithianyl, oxazinyl, e.g. 2*H*-1,3-, 6*H*-1,3-, 6*H*-1,2-, 2*H*-1,2- or 4*H*-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. *o*- or *p*-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-, oxadiazinyl groups.

Cycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon atom. Heterocycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon or, where available, ring nitrogen atom.

For the case where NR^4R^5 represents an optionally substituted heterocycloaliphatic ring, the heterocyclic moiety must contain at least one nitrogen atom. This includes, for example, azetidiny, pyrrolidinyl, piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl, N - C_{1-6} alkylpiperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl and the like.

The NR^4R^5 heterocycloaliphatic ring may optionally be fused to an optionally substituted monocyclic C_{6-12} aromatic group, such as phenyl or an optionally substituted monocyclic C_{1-9} heteroaromatic group containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms.

The optional substituents which may be present on the aliphatic, alkyl, alkenyl, alkynyl, cycloaliphatic or heterocycloaliphatic groups, described above and generally herein include one, two, three or more substituents, which each may be the same or different, selected from halogen atoms, or alkoxy, haloalkyl, haloalkoxy, hydroxy (-OH), thiol (-SH), alkylthio, amino (-NH₂), substituted amino, optionally substituted C_{6-12} arylamino, -CN, -CO₂H, -CO₂R¹¹ (where R¹¹ is an optionally substituted C_{1-6} alkyl group), -SO₃H, -SOR¹² (where R¹² is a C_{1-6} alkyl group), -SO₂R¹², -SO₃R¹², -OCO₂R¹², -C(O)H, -C(O)R¹², -OC(O)R¹², -C(S)R¹², -C(O)N(R¹³)(R¹⁴) (where R¹³ and R¹⁴, which may be the same or different is each a hydrogen atom or a C_{1-6} alkyl group), -OC(O)N(R¹³)(R¹⁴), -N(R¹³)C(O)R¹⁴, -CSN(R¹³)(R¹⁴), -N(R¹³)C(S)(R¹⁴), -SO₂N(R¹³)(R¹⁴), -N(R¹³)SO₂R¹⁴, -N(R¹³)C(O)N(R¹⁴)(R¹⁵) (where R¹⁵ is a hydrogen atom or a C_{1-6} alkyl group), -N(R¹³)C(S)N(R¹⁴)(R¹⁵), -N(R¹³)SO₂N(R¹⁴)(R¹⁵), or an optionally substituted aromatic or heteroaromatic group or a C_{1-6} alkyl group optionally substituted by one, two, three or more of the same or different halogen atoms, or alkoxy, haloalkyl,

haloalkoxy, hydroxy (-OH), thiol (-SH), alkylthio, amino (-NH₂), substituted amino, optionally substituted C₆₋₁₂arylamino, -CN, -CO₂H, -CO₂R¹¹, -SO₃H, -SOR¹², -SO₂R¹², -SO₃R¹², -OCO₂R¹², -C(O)H, -C(O)R¹², -OC(O)R¹², -C(S)R¹², -C(O)N(R¹³)(R¹⁴), -OC(O)N(R¹³)(R¹⁴), -N(R¹³)C(O)R¹⁴,
 5 -CSN(R¹³)(R¹⁴), -N(R¹³)C(S)(R¹⁴), -SO₂N(R¹³)(R¹⁴), -N(R¹³)SO₂R¹⁴, -N(R¹³)C(O)N(R¹⁴)(R¹⁵), -N(R¹³)C(S)N(R¹⁴)(R¹⁵), -N(R¹³)SO₂N(R¹⁴)(R¹⁵) or optionally substituted aromatic or heteroaromatic groups. Substituted amino groups include -NHR¹² and -N(R¹²)(R¹³) groups.

- 10 The optional substituents which may be present on aliphatic chains represented by Alk¹ or Alk² include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CO₂H, -CO₂R¹⁶ [where R¹⁶ is an optionally substituted straight or branched C₁₋₆ alkyl group], e.g.
 15 -CO₂CH₃ or -CO₂C(CH₃)₃, -CONHR¹⁶, e.g. -CONHCH₃, -CON(R¹⁶)₂, e.g. -CON(CH₃)₂, -COR¹⁶, e.g. -COCH₃, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol (-SH), -S(O)R¹⁶, e.g. -S(O)CH₃, -S(O)₂R¹⁶, e.g. -S(O)₂CH₃, C₁₋₆alkylthio e.g. methylthio or ethylthio, amino, -NHR¹⁶, e.g. -NHCH₃ or -N(R¹⁶)₂, e.g. -N(CH₃)₂ groups.
 20 Where two R¹⁶ groups are present in any of the above substituents these may be the same or different.

When R¹⁰, R¹², R¹³, R¹⁴, R¹⁵ or R¹⁶ is present as a C₁₋₆alkyl group it may be a straight or branched C₁₋₆ alkyl group e.g. a C₁₋₃ alkyl group such as methyl, ethyl or i-propyl. Optional substituents which may be present on R¹⁶ include
 25 for example one, two or three substituents which may be the same or different selected from fluorine, chlorine, bromine or iodine atoms or hydroxy or C₁₋₆ alkoxy e.g. methoxy or ethoxy groups.

30 When L¹ is present in compounds of formula (1) as a linker atom or group it may be any such atom or group as hereinbefore described in relation to L² linker atoms and groups. When in compounds of this type Alk¹ is a covalent

bond then L¹ is a -C(O)-, -C(O)O-, -C(S)-, -S(O)₂-, -CON(R¹⁰)-, -CSN(R¹⁰)- or -S(O)₂N(R¹⁰)- group, where R¹⁰ is as herein defined.

5 The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include -CF₃, -CCl₃, -CHF₂, -CHCl₂,
10 -CH₂F, and -CH₂Cl groups.

The term "alkoxy" as used herein is intended to include straight or branched C₁₋₁₀alkoxy for example C₁₋₆alkoxy such as methoxy, ethoxy, *n*-propoxy, *i*-propoxy and *t*-butoxy. "Haloalkoxy" as used herein includes any of those
15 alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include -OCF₃, -OCCl₃, -OCHF₂, -OCHCl₂, -OCH₂F and -OCH₂Cl groups.

As used herein the term "alkylthio" is intended to include straight or branched
20 C₁₋₁₀alkylthio, e.g. C₁₋₆alkylthio such as methylthio or ethylthio groups.

The terms "aromatic group" and "aryl group" are intended to include for example optionally substituted monocyclic ring C₆₋₁₂ aromatic groups, such as phenyl, or bicyclic fused ring C₆₋₁₂ aromatic groups, such as, 1- or 2-naphthyl
25 groups.

The terms "heteroaromatic group" and "heteroaryl group" are intended to include for example optionally substituted C₁₋₉ heteroaromatic groups containing for example one, two, three or four heteroatoms selected from
30 oxygen, sulfur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Bicyclic heteroaromatic

groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulfur or nitrogen atoms.

- 5 Each of these aromatic or heteroaromatic groups may be optionally substituted by one, two, three or more R^{17} atoms or groups as defined below.

Particular examples of monocyclic ring heteroaromatic groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, N - C_{1-6} alkylimidazolyl, oxazolyl,
 10 isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, or triazinyl.

Particular examples of bicyclic ring heteroaromatic groups of this type include benzofuryl, benzothieryl, benzotriazolyl, indolyl, indazolyl, benzimidazolyl,
 15 imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl or phthalazinyl.

- 20 The R^2 or R^9 heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

Optional substituents which may be present on the aromatic or heteroaromatic
 25 groups include one, two, three or more substituents, each selected from an atom or group R^{17} in which R^{17} is $-R^{17a}$ or $-\text{Alk}^3(R^{17a})_i$, where R^{17a} is a halogen atom, or an amino ($-\text{NH}_2$), substituted amino, nitro, cyano, hydroxyl ($-\text{OH}$), substituted hydroxyl, amidino, formyl, carboxyl ($-\text{CO}_2\text{H}$), esterified carboxyl, thiol ($-\text{SH}$), substituted thiol, $-\text{COR}^{18}$ [where R^{18} is an $-\text{Alk}^3(R^{17a})_i$,
 30 heterocycloaliphatic, cycloaliphatic, aryl or heteroaryl group], $-\text{CSR}^{18}$, $-\text{SO}_3\text{H}$, $-\text{SOR}^{18}$, $-\text{SO}_2\text{R}^{18}$, $-\text{SO}_3\text{R}^{18}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHR}^{18}$, $\text{SO}_2\text{N}(R^{18})_2$, $-\text{CONH}_2$, $-\text{CSNH}_2$, $-\text{CONHR}^{18}$, $-\text{CSNHR}^{18}$, $-\text{CON}(R^{18})_2$, $-\text{CSN}(R^{18})_2$, $-\text{N}(R^{19})\text{SO}_2\text{R}^{18}$, [where R^{19} is a hydrogen atom or an alkyl group] $-\text{N}(\text{SO}_2\text{R}^{18})_2$.

-N(R¹⁹)SO₂NH₂, -N(R¹⁹)SO₂NHR¹⁸, -N(R¹⁸)SO₂N(R¹⁹)₂, -N(R¹⁹)COR¹⁸,
 -N(R¹⁹)CONH₂, -N(R¹⁹)CONHR¹⁸, -N(R¹⁹)CON(R¹⁸)₂, -N(R¹⁹)CSNH₂,
 -N(R¹⁹)CSNHR¹⁸, -N(R¹⁹)CSN(R¹⁸)₂, -N(R¹⁹)CSR¹⁸, -N(R¹⁹)C(O)OR¹⁸,
 -SO₂NHet¹ [where -NHet¹ is an optionally substituted C₅₋₇cyclicamino group
 5 optionally containing one or more other -O- or -S- atoms or -N(R¹⁹)-, -C(O)- or
 -C(S)- groups], -CONHet¹, -CSNHet¹, -N(R¹⁹)SO₂NHet¹, -N(R¹⁹)CONHet¹,
 -N(R¹⁹)CSNHet¹, -SO₂N(R¹⁹)Het² [where Het² is an optionally substituted
 monocyclic C₅₋₇carbocyclic group optionally containing one or more -O- or -S-
 atoms or -N(R¹⁹)-, -C(O)- or -C(S)- groups], -Het², -CON(R¹⁹)Het²,
 10 -CSN(R¹⁹)Het², -N(R¹⁹)CON(R¹⁹)Het², -N(R¹⁹)CSN(R¹⁹)Het², aryl or heteroaryl
 group; Alk³ is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆
 alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms
 or -S(O)_g- [where g is an integer 1 or 2] or -N(R¹⁹)- groups; and f is zero or an
 integer 1, 2 or 3. It will be appreciated that when two R¹⁸ or R¹⁹ groups are
 15 present in one of the above substituents, the R¹⁸ or R¹⁹ groups may be the
 same or different.

When in the group -Alk³(R^{17a})_f, f is an integer 1, 2 or 3, it is to be understood
 that the substituent or substituents R^{17a} may be present on any suitable
 20 carbon atom in -Alk³. Where more than one R^{17a} substituent is present these
 may be the same or different and may be present on the same or different
 atom in -Alk³. Clearly, when f is zero and no substituent R^{17a} is present the
 chain represented by Alk³ becomes a corresponding group.

25 When R^{17a} is a substituted amino group it may be for example a group
 -NHR¹⁸ [where R¹⁸ is as defined above] or a group -N(R¹⁸)₂ wherein each R¹⁸
 group is the same or different.

When R^{17a} is a substituted hydroxyl or substituted thiol group it may be for
 30 example a group -OR¹⁸ or a -SR¹⁸ group respectively.

Esterified carboxyl groups represented by the group R^{17a} include groups of
 formula -CO₂Alk⁴ wherein Alk⁴ is an optionally substituted alkyl group.

When Alk³ is present in or as a substituent it may be for example a methylene, ethylene, *n*-propylene, *i*-propylene, *n*-butylene, *i*-butylene, *s*-butylene, *t*-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R¹⁹)- groups.

When -NHet¹ or -Het² forms part of a substituent R¹⁷ each may be for example an optionally substituted 2- or 3-pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperazinyl, imidazolinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those substituents described above in relation to aromatic groups.

Particularly useful atoms or groups represented by R¹⁷ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl or *t*-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl or piperidinyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, aminoC₁₋₆alkylamino e.g. aminoethylamino, Het¹NC₁₋₆alkylamino e.g. morpholinopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋

- ₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino e.g. hydroxyethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, formyl [HC(O)-], carboxyl (-CO₂H), -
- 5 CO₂Alk⁴ [where Alk⁴ is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), -SO₃R¹⁸, C₁₋₆alkylsulphinyl e.g. methylsulphinyl, C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylamino-sulphonyl or
- 10 ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethyl-aminosulphonyl or diethylaminosulphonyl, optionally substituted phenylamino-sulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylamino-carbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethyl-aminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g.
- 15 aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylamino-carbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylamino-
- 20 carbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkyl-
- 25 sulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g.
- 30 dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g.

- acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkyl-aminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, 5 ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, benzylamino, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.
- 10 Where desired, two R¹⁷ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

- It will be appreciated that where two or more R¹⁷ substituents are present, 15 these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group.

- The presence of certain substituents in the compounds of formula (1) may 20 enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

- 25 Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, 30 succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium

or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include
5 pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

Examples of optionally substituted alkyl groups present in ester groups of formulae $-\text{CO}_2\text{R}^{11}$ and $-\text{CO}_2\text{Alk}^4$ include C_{1-6} alkyl groups as herein described,
10 in particular C_{1-3} alkyl groups. Optional substituents, which may be present on these alkyl groups, include optionally substituted cycloaliphatic, aromatic or heteroaromatic groups as herein defined. Particular examples include optionally substituted C_{3-6} cycloalkyl wherein the optional substituents include for example one, two or three substituents which may be the same or different
15 selected from fluorine, chlorine, bromine or iodine atoms or hydroxy or C_{1-6} alkoxy e.g. methoxy or ethoxy groups; or optionally substituted phenyl or five or six membered heteroaryl groups wherein the optional substituents include for example one, two or three substituents which may be the same or different selected from fluorine, chlorine, bromine, straight or branched C_{1-6} alkyl,
20 methoxy, OCF_3 , OCF_2H , CF_3 , CN , NHCH_3 , $\text{N}(\text{CH}_3)_2$, CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CO_2CH_3 , $\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2\text{C}(\text{CH}_3)_3$, or $-\text{COCH}_3$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$ or CO_2H .

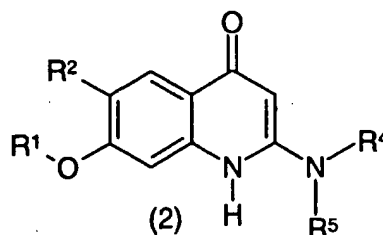
Examples of alkyl groups, represented by R^3 , R^5 , R^6 , R^7 or R^8 include C_{1-6} alkyl
25 groups as herein described. More particular examples include C_{1-3} alkyl groups, such as $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$ or $-\text{CH}(\text{CH}_3)\text{CH}_3$.

One particular group of compounds of the invention has the formula (1)
wherein X is an O atom.

30

A particular group of compounds has the formula (1) wherein R^3 is a hydrogen atom or a $-\text{CN}$ group, especially a hydrogen atom.

A particularly useful group of compounds of the invention has the formula (2):



wherein R¹, R², R⁴ and R⁵ are as defined herein for compounds of formula (1); and the salts, solvates, hydrates, tautomers, isomers or *N*-oxides thereof.

5

Examples of aliphatic groups, represented by R¹ include C₁₋₆ alkyl groups as herein described. More particular examples include C₁₋₃ alkyl groups, such as -CH₃, -CH₂CH₃, -CH₂CH₂CH₃ or -CH(CH₃)CH₃. Examples of cycloaliphatic groups which may represent R¹ include C₃₋₆ cycloalkyl groups, such as those described previously. Examples of cycloalkyl-alkyl- groups which may represent R¹ include C₁₋₃ alkyl groups (as described herein) where a terminal hydrogen atom is replaced by a C₃₋₆ cycloalkyl ring (as described herein), for example, cyclopropylCH₂-.

10

15 In one group of compounds of formulae (1) or (2) R¹ is in particular a C₁₋₆ alkyl group. Especially preferred is when R¹ is a C₁₋₃ alkyl group. Most especially preferred is when R¹ is a methyl group.

In another group of compounds of formulae (1) or (2) R¹ is in particular a haloalkyl group. Especially preferred is when R¹ is a -CHF₂ or -CH₂F group.

20

One group of compounds has the formulae (1) or (2) wherein R² is a -CN group.

25 Another group of compounds of the invention has the formulae (1) or (2) wherein R² is an optionally substituted heteroaromatic group. In particular R² is an optionally substituted monocyclic ring heteroaromatic, especially a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Particular

heteroaromatic groups which may represent R^2 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, *N*- C_{1-6} alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, ozadiazolyl, thiadiazolyl, triazolyl or pyrazolyl. Especially preferred is when R^2 is an oxazolyl group.

5

Particular examples of the group R^4 , in compounds of formulae (1) or (2), include $-Alk^1-L^1-Alk^2-R^9$, $-Alk^1-L^1-R^9$, $-Alk^1-R^9$, $-L^1-Alk^2-R^9$, $-L^1-R^9$ or $-R^9$ wherein Alk^1 , L^1 , Alk^2 and R^9 are as herein defined. R^4 in one group of compounds of formulae (1) or (2) is the chain $-Alk^1-L^1-R^9$. R^4 is preferably the chain $-Alk^1-R^9$.

10

Alk^1 , when present in compounds of formulae (1) or (2), is preferably an optionally substituted aliphatic chain, in particular a C_{1-6} alkylene chain, especially an optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ chain, most especially a C_{1-3} alkylene chain such as a $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ chain.

15

Particular examples of L^1 , when present in compounds of formulae (1) or (2), include $-O-$ or $-S-$ atoms or $-C(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{10})-$ [where R^{10} is as defined hereinbefore], $-CON(R^{10})-$, $-CSN(R^{10})-$, $-N(R^{10})CO-$, $-N(R^{10})CS-$, $-S(O)_2N(R^{10})-$ or $-N(R^{10})S(O)_2-$ groups. R^{10} is especially a hydrogen atom or a C_{1-3} alkyl group, particularly a methyl group.

20

One group of compounds of the invention has the formulae (1) or (2) wherein Alk^1 is an optionally substituted aliphatic chain, L^1 and Alk^2 are each a covalent bond and R^9 is a hydrogen atom. In compounds of this type Alk^1 is in particular an optionally substituted C_{1-6} alkylene chain. In one particular group of compounds of this class R^4 is especially a straight or branched C_{1-6} alkyl group, particularly $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$ or $-C(CH_3)_3$. In another particular group of compounds of this class Alk^1 is a substituted C_{1-6} alkylene chain, especially $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$ or $-CH_2C(CH_3)_2-$.

30

Particular substituents present on the groups Alk^1 or Alk^2 include $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{16}$ [where R^{16} is as herein defined] $-\text{CONHR}^{16}$, $-\text{CON}(\text{R}^{16})_2$, $-\text{COR}^{16}$, C_{1-6} alkoxy, particularly methoxy or ethoxy; halo C_{1-6} alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-\text{S}(\text{O})\text{R}^{16}$, $-\text{S}(\text{O})_2\text{R}^{16}$, amino, $-\text{NHR}^{16}$ or $-\text{N}(\text{R}^{16})_2$ groups. R^{16} is in particular a C_{1-3} alkyl group.

Another group of compounds of the invention has the formulae (1) or (2) wherein Alk^1 is an optionally substituted aliphatic chain, L^1 and Alk^2 are each a covalent bond and R^9 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. Particular compounds of this type are those wherein R^9 is an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group. Particular R^9 examples include optionally substituted azetidiny, pyrrolidinyl, pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, N-C_{1-6} alkylpiperazinyl, especially $\text{N-methylpiperazinyl}$, N-C_{1-6} alkylpyrrolidinyl, especially $\text{N-methylpyrrolidinyl}$, N-C_{1-6} alkylpiperidinyl, especially $\text{N-methylpiperidinyl}$, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6} alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl or triazinyl. In this group of compounds Alk^1 is in particular a C_{1-3} alkylene chain, especially $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$. R^9 in general in these compounds is especially an optionally substituted aromatic or heteroaromatic group. In another particular group of compounds of this type R^9 is an optionally substituted cycloaliphatic group especially a C_{3-6} cycloalkyl group.

A further group of compounds of the invention has the formulae (1) or (2) wherein Alk^1 , Alk^2 and L^1 are each a covalent bond and R^9 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. One preferred group of compounds is where R^9 is an optionally substituted phenyl or monocyclic heteroaromatic group. In compounds of this type R^9 is in particular an optionally substituted phenyl, pyridyl, pyrimidinyl,

pyridazinyl or pyrazinyl group especially an optionally substituted phenyl or pyridyl group. R⁹ in one group of compounds is a phenyl or pyridyl group.

5 R⁵ in compounds of the invention is especially a hydrogen atom or a methyl group, particularly a hydrogen atom.

Another useful group of compounds of the invention has the formulae (1) or (2) wherein NR⁴R⁵ forms an optionally substituted heterocycloaliphatic group. In compounds of this type NR⁴R⁵ is in particular an optionally substituted
10 azetidinyll or optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, N-C₁₋₆alkylpiperazinyl, homopiperazinyl, morpholinyl or thiomorpholinyl group, especially a morpholinyl group. NR⁴R⁵ is also in particular an optionally substituted pyrrolidinyl or piperidinyl group. These groups may be fused to an optionally substituted monocyclic C₆₋₁₂aromatic group, such as phenyl or an
15 optionally substituted monocyclic C₁₋₉heteroaromatic group containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. In particular NR⁴R⁵ is fused to an optionally substituted phenyl or five or six membered heteroaryl group. Particular examples of heteroaryl groups include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl,
20 oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, especially pyridyl, pyrimidinyl or pyridazinyl. In one particular group of compounds NR⁴R⁵ is fused to an optionally substituted phenyl group and may in particular be an optionally substituted 2,3-dihydro-1*H*-indolyl, 2,3-dihydro-1*H*-isoindolyl,
25 1,2,3,4 tetrahydroquinolinyl or 1,2,3,4 tetrahydroisoquinolinyl group.

One group of optional substituents which may be present on aromatic or heteroaromatic groups in compounds of formulae (1) or (2) and in particular in R⁹ aromatic or heteroaromatic groups or in the aryl or heteroaryl groups
30 optionally fused to NR⁴R⁵ include one, two, three or more atoms or groups selected from fluorine, chlorine, bromine, straight or branched C₁₋₆ alkyl, methoxy, OCF₃, OCF₂H, CF₃, CN, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃, CON(CH₃)₂, CO₂CH₃, CO₂CH₂CH₃, -CO₂C(CH₃)₃, or -COCH₃, -NHCOCH₃,

-N(CH₃)COCH₃ or CO₂H or optionally substituted morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl wherein the optional substituent are as herein defined.

- 5 One group of optional substituents which may be present on cycloaliphatic or heterocycloaliphatic groups in compounds of formulae (1) or (2) and in particular on the groups R⁹ or NR⁴R⁵, are one, two, three or more groups selected from C₁₋₃ alkoxy, OCF₃, OCF₂H, CF₃, C₁₋₃ alkylthio, -CN, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃, CON(CH₃)₂, CO₂CH₃, CO₂CH₂CH₃,
 10 -CO₂C(CH₃)₃, -COCH₃, -NHCOCH₃, -N(CH₃)COCH₃, CO₂H, or optionally substituted straight or branched C₁₋₃ alkyl, wherein the optional alkyl substituent is in particular -CN, C₁₋₃ alkoxy, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃, CON(CH₃)₂, CO₂CH₃, CO₂CH₂CH₃, -CO₂C(CH₃)₃, -COCH₃, -NHCOCH₃, -N(CH₃)COCH₃ or CO₂H.

15

When compounds of formulae (1) or (2) contain a heterocycloaliphatic or heteroaryl group having an available N atom this may in particular be substituted with an optionally substituted straight or branched C₁₋₃ alkyl group, especially a methyl group.

20

Particular compounds of the invention include:

- 2-(2,3-Dihydroindol-1-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
 2-(Dihydro-1*H*-isoquinolin-2-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
 2-(1,3-Dihydroisoindol-2-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
 25 2-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
 2-(5-Bromo-2,3-dihydroindol-1-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
 7-Methoxy-2-(2-methyl-2,3-dihydroindol-1-yl)-6-oxazol-5-yl-1*H*-quinolin-4-one;
 7'-Methoxy-6'-oxazol-5-yl-3,4-dihydro-2*H*,1'*H*-[1,2']biquinoliny-4'-one;
 30 and the salts, solvates, hydrates, tautomers, isomers or *N*-oxides thereof.

Compounds of formulae (1) or (2) are potent inhibitors of IMPDH. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

5 Thus the compounds of the invention may be used in the treatment of IMPDH-associated disorders. The invention extends to such a use and in general to the use of the compounds of formulae (1) or (2) for the manufacture of a medicament for treating such diseases and disorders.

10 "IMPDH-associated disorders" refers to any disorder or disease state in which inhibition of the enzyme IMPDH (inosine monophosphate dehydrogenase, EC1.1.1.205, of which there are presently two known isozymes referred to as IMPDH type 1 and IMPDH type 2) would modulate the activity of cells (such as lymphocytes or other cells) and thereby ameliorate or reduce the
15 symptoms or modify the underlying cause(s) of that disorder or disease. There may or may not be present in the disorder or disease an abnormality associated directly with the IMPDH enzyme. Examples of IMPDH-associated disorders include transplant rejection and autoimmune disorders, such as rheumatoid arthritis, lupus, multiple sclerosis, juvenile diabetes, asthma, and
20 inflammatory bowel disease, as well as inflammatory disorders, cancer and tumors, T-cell mediated hypersensitivity diseases, ischemic or reperfusion injury, viral replication diseases, proliferative disorders and vascular diseases.

Use of the compounds of the present invention is exemplified by, but is not
25 limited to, treating a range of disorders such as: treatment of transplant rejection (e.g. kidney, liver, heart, lung, pancreas (e.g., islet cells), bone marrow, cornea, small bowel, skin allografts, skin homografts (such as employed in burn treatment), heart valve xenografts, serum sickness, and graft vs. host disease, in the treatment of autoimmune diseases, such as
30 rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), pyoderma gangrenum, lupus (systemic lupus erythematosus), myasthenia gravis, psoriasis, eczema, dermatitis, dermatomyositis, atopic dermatitis; multiple sclerosis, seborrhoea, pulmonary inflammation, eye

uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular
5 disease (also known as autoimmune polyglandular syndrome) glomerulonephritis, scleroderma, morphea, lichen planus, viteligo (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituitarism, cicatricial pemphigoid, Gullivan-Barre syndrome, and alveolitis; in the treatment of T-cell mediated hypersensitivity
10 diseases, including contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis (including that due to poison ivy), urticaria, skin allergies, respiratory allergies (hayfever, allergic rhinitis) and gluten-sensitive enteropathy (Celiac disease); in the treatment of inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, acute
15 respiratory distress syndrome, Sezary's syndrome and vascular diseases which have an inflammatory and or a proliferatory component such as restenosis, stenosis and arteriosclerosis; in the treatment of cancer and tumor disorders, such as solid tumors, lymphomas and leukemia; in the treatment of fungal infections such as mycosis fungoides; in protection from
20 ischemic or reperfusion injury such as ischemic or reperfusion injury that may have been incurred during organ transplantation, myocardial infarction, stroke or other causes; in the treatment of DNA or RNA viral replication diseases, such as herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, Epstein-Barr,
25 human immunodeficiency virus (HIV) and influenza.

Additionally, IMPDH is also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds of the present invention may be useful in treatment or prevention of bacterial
30 infection, alone or in combination with other antibiotic agents.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the afore mentioned exemplary disorders irrespective of

their etiology, for example, for the treatment of lupus, psoriasis, inflammatory bowel disease, multiple sclerosis, atopic dermatitis or rheumatoid arthritis.

5 In another particular embodiment the compounds of the present invention are of particular use for the treatment of DNA or RNA viral replication diseases, such as hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, human immunodeficiency virus (HIV) and influenza.

10 In an additional particular embodiment the compounds of the present invention are of particular use for the treatment of cancer and tumour disorders, such as solid tumors, lymphoma, leukemia and other forms of cancer.

15 The compounds of formulae (1) or (2) can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, anti-inflammatory agents, antibiotics and immunosuppressants for the treatment or prophylaxis of transplant rejection and autoimmune disease.

20 For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formulae (1) or (2) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

25 Alternate compositions of this invention comprise a compound formula (1) or a salt thereof; an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, anti-fungal agent, anti-vascular hyperproliferation agent or an antibiotic agent; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

30

Thus, for example, additional immunosuppression agents include, but are not limited to, cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, OKT3, ATAG, interferon and mizoribine. Additional anti-vascular hyperproliferative agents include, but are not limited to, HMG

Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, ciprostone, trapidil, eicosapentanoic acid, ACE inhibitors, low molecular weight heparin, and rapamycin. Additional anti-cancer agents include, but are not limited to, cis-platin, actinomycin D, amsacrine, mitoxantrone, doxorubicin, vincristine, vinblastine, etoposide, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioxantheres. Additional anti-viral agents include, but are not limited to, Cytovene, Ganiclovir, trisodium phosphonoformate, Ribavirin, d4T, ddl, AZT and acyclovir.

10

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in amounts generally indicated for use in standard formularies (e.g. in the Physician's Desk Reference (PDR)) or as determined using routine pharmaceutical dosing methods.

15

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, vaginal or rectal administration, or a form suitable for administration by inhalation or insufflation.

20

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents,

30

emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

- 5 Preparations for oral administration may be suitably formulated to give controlled release of the active compound

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

10

The compounds for formulae (1) or (2) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take
15 such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of
20 formulae (1) or (2) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formulae (1) or (2) may also be formulated as a depot preparation. Such long acting
25 formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form
30 of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds of formulae (1) or (2) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for
5 example cocoa butter and polyethylene glycols.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by
10 instructions for administration.

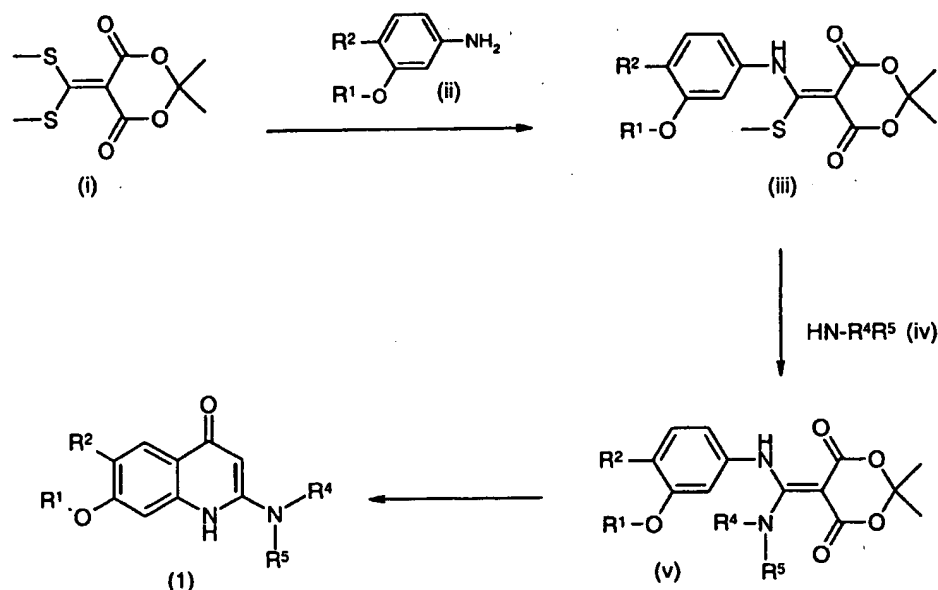
The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however,
15 daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

20 The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as
25 such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

In the following process description, the symbols R^1 - R^5 when used in the formulae depicted are to be understood to represent those groups described
30 above in relation to formulae (1) or (2) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with

standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formulae (1) or (2) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

For example, a compound of formulae (1) or (2) where X is an O atom and R³ is a hydrogen atom may be prepared by following the general route as shown in Scheme A:

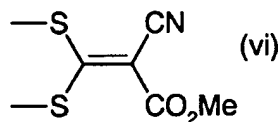


Scheme A

A quinolone of general formula (1) may be prepared using similar methodology to that reported by Bang-Chi *et al* (*Synthesis*, pp. 317-320, (1989)). Thus commercially available 5-(bismethylsulfanylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (i) may be treated with an amine of general formula (ii) to give a malonate of general formula (iii). Appropriate conditions for this reaction may involve heating in an alcoholic solvent e.g. ethanol at reflux temperature for a suitable period of time e.g. 2 hours. The malonate (iii) may then be treated with an amine of general formula (iv) using appropriate conditions, for example, in the presence of mercury (II) chloride at room

temperature or with heating, to afford a compound of general formula (v). The reaction may be performed without solvent (for example, if one of the reagents is a liquid) or in the presence of a small amount of a suitable solvent e.g. tetrahydrofuran, DMF or diphenyl ether. The compound of formula (v) may then be cyclised, for example, by heating in a solvent such as diphenyl ether at the reflux temperature in to afford a quinolone of formula (1) wherein R³ is a hydrogen atom. The cyclisation may also be performed in a microwave reactor in for example diphenyl ether in the presence of a co-solvent such as N-methylpyrrolidinone. Alternatively the compound of formula (iii) may be converted to a compound of formula (1) in a one-pot reaction without the need to isolate a compound of formula (v) using similar methodology as described above.

Alternatively when R³ in compounds of formula (1) is a -CN group, compounds of this type may be prepared in a similar manner to the general route described for Scheme A. See also Tominaga *et al* J. of Heterocyclic Chem. 27, (5), pp.1217-1225, (1990). Thus instead of using the compound of formula (i) commercially available 2-cyano-3,3-bis-methylsulfanylacrylic acid methyl ester (vi):



may be reacted with an amine of general formula (ii) employing the same methodology as described in Scheme A. The intermediate thus formed may be further manipulated using the same methods as described above and an amine of formula (iv) to afford a compound of formula (1) wherein R³ is a -CN group.

When R³ in compounds of formula (1) is a -CO₂H, -CO₂R⁶ or -CONR⁷R⁸ group such compounds may be prepared from the corresponding compound of formula (1) where R³ is a -CN group using standard conditions known to those skilled in the art. Thus, nitrile (CN) groups may be hydrolysed in the presence of acid or base to give an acid or primary amide using standard

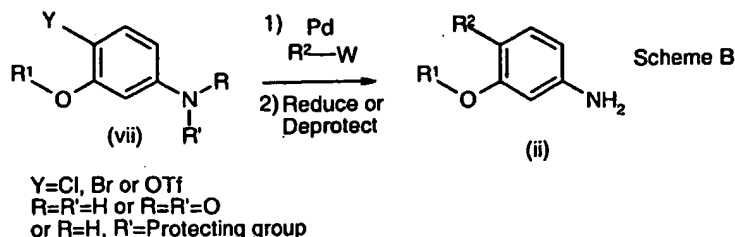
methods. The groups thus formed may then be further functionalised using standard alkylation and esterification techniques.

5 Compounds of formula (1) in which X is an O atom may be converted to their thio ketone analogues using standard techniques, for example, by reaction with Lawesson's reagent in a suitable solvent, such as tetrahydrofuran or toluene.

10 Intermediates of formulae (ii) and (iv) and any other intermediates required to obtain compounds of formulae (1) and (2), if not available commercially, may be prepared by methods known to those skilled in the art following procedures set forth in references such as Rodd's Chemistry of Carbon Compounds, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-19 (John Wiley and
15 Sons, 1999), Comprehensive Heterocyclic Chemistry, Ed. Katritzky et al, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), Comprehensive Organic Functional Group Transformations, Ed. Katritzky et al, Volumes 1-7, 1995 Pergamon), Comprehensive Organic Synthesis, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), Encyclopaedia of Reagents for
20 Organic Synthesis Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and March's Advanced Organic Chemistry (John Wiley and Sons, 1992).

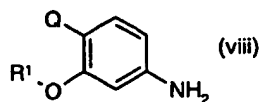
25 Thus amines of general formula (ii) may be prepared in a variety of ways. For example, the compound of formula (iii) where R^1 is a methyl group and R^2 is an oxazole group may be prepared using methods known in the literature (CAS 198821-79-3).

30 Alternatively amines of formula (ii), where R^2 is an optionally substituted heteroaromatic group, may be prepared using the route as shown in Scheme B:



For example, a compound of formula (vii), where Y is a halogen atom e.g. Cl or Br or a suitable leaving group e.g. trifluoromethylsulfonyloxy (OTf) and –NRR' is a nitro group or an amine group (which may be suitably protected), may be reacted with a derivative of the desired heteroaromatic group (R²-W, where W is as described below) utilising a palladium catalysed cross coupling reaction. The following literature methodology may be used to perform this coupling reaction according to the nature of the W group; e.g. when W is a hydrogen atom (Heterocycles, 31, pp. 1951-1958, (1990)); the zinc species (W=ZnCl) (J Organomet. Chem., 390, pp. 389-398, (1990); Tetrahedron, 53, pp. 7237-7254, (1997)); the mercury species (W=HgBr) (Chem. Heterocycl. Compd., 19, pp. 1159-1162, (1983)) or a boron derivative (W=B(OH)₂, W=BEt₂) (J. Med. Chem., 40, pp. 3542-3550, (1997); J. Org. Chem., 63, pp. 8295-8303, (1998)). The resulting coupled product may require further manipulation, depending on the nature of the –NRR' group, in order to obtain an amine of formula (ii). For example, when –NRR' is a nitro group this may be reduced to an amine using standard techniques, or when –NRR' is a protected amine the protecting group may be removed using standard methodology. It will be appreciated that the various R²-W derivatives are either commercially available or may be prepared using methods known to those skilled in the art. In a similar manner the compounds of formula (vii) are either commercially available or may be prepared using methods known to those skilled in the art. For example, the compound of formula (vii) may be prepared by alkylation of the phenol precursor of (vii) using standard techniques.

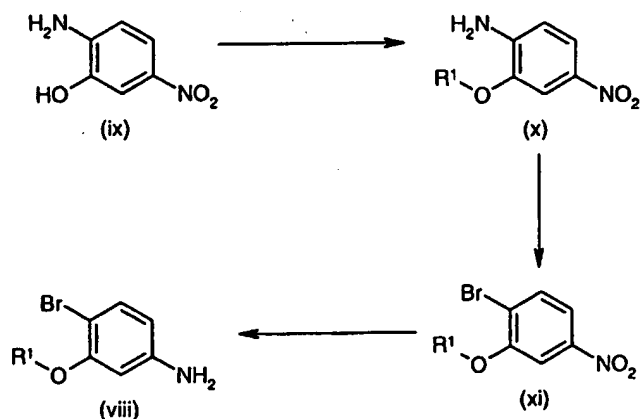
When R² in compounds of formula (1) is a –CN group, these may be prepared using similar methodology to that described herein starting from a compound of formula (viii):



wherein Q is a halogen atom e.g. bromine or a protected phenol e.g. *tert*-butyldimethylsilyloxy group. Thus an amine of formula (viii) may be used instead of the amine of formula (ii) in the general route as shown in Scheme

- 5 A. The quinolone thus formed may then be further converted using methods known to those skilled in the art to give a compound of formula (1) wherein R² is a CN group. For example, when Q is a bromine atom this may be reacted with a cyanide group e.g. zinc cyanide in the presence of a palladium catalyst e.g. tetrakis(triphenylphosphine) palladium (0) in for example *N,N*-
 10 dimethylformamide at 100°C. Alternatively when Q is a protected phenol group this may, after deprotection, be converted into a leaving group e.g. trifluoromethylsulfonyloxy and displaced in a similar manner to that as described above for the bromide.

- 15 An amine of formula (viii) may be prepared using standard methods known to those skilled in the art. For example when Q is a bromine atom this may be prepared using the general route as shown in Scheme C:



Scheme C

- Thus the commercially available compound of formula (ix) may be alkylated e.g. using a reagent R¹Y (where Y is as defined earlier) in the presence of a
 20 base, at the phenol position using standard methodology to give a compound of formula (x). The compound of formula (x) may then be converted to a bromide of formula (xi) using methods known to those skilled in the art, for example by treatment with sodium nitrite in the presence of aqueous

hydrogen bromide followed by the addition of copper bromide and hydrogen bromide. The compound of formula (viii) may then be prepared by reduction of the nitro group in the compound of formula (xi) using for example palladium catalysed hydrogenation.

5

It will be appreciated that compounds of formula (1) or any preceding intermediates such as intermediates of formula (iv) may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include
10 conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of any of formula (1) or any preceding intermediates where appropriate functional groups exist in these compounds.

15

For example, ester groups such as $-\text{CO}_2\text{R}^{11}$ or $-\text{CO}_2\text{Alk}^4$ in the compounds may be converted to the corresponding acid $[-\text{CO}_2\text{H}]$ by acid- or base-catalysed hydrolysis depending on the nature of the groups R^{11} or Alk^4 . Acid- or base- catalysed hydrolysis may be achieved for example by treatment with
20 an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol. Similarly an acid $[-\text{CO}_2\text{H}]$ may be prepared by hydrolysis of the corresponding nitrile $[-\text{CN}]$, using for example a base such as sodium
25 hydroxide in a refluxing alcoholic solvent, such as ethanol.

In another example, $-\text{OH}$ groups may be generated from the corresponding ester [e.g. CO_2Alk^4 or CO_2R^{11}] or aldehyde $[-\text{CHO}]$ by reduction, using for example a complex metal hydride such as lithium aluminium hydride in diethyl
30 ether or tetrahydrofuran or sodium borohydride in a solvent such as methanol. Alternatively an alcohol may be prepared by reduction of the corresponding acid $[-\text{CO}_2\text{H}]$, using for example lithium aluminium hydride in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. *p*-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol
5 may be reacted with thionyl chloride in a halogenated hydrocarbon e.g., dichloromethane to yield the corresponding chloride. A base e.g., triethylamine may also be used in the reaction.

In another example, alcohol or phenol groups may be converted to ether groups
10 by coupling a phenol with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate. Alternatively ether groups may be prepared by deprotonation of an alcohol, using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as
15 an alkylhalide.

Aldehyde [-CHO] groups may be obtained by oxidation of a corresponding alcohol using well-known conditions. For example using an oxidising agent such as a periodinane e.g. Dess Martin, in a solvent such as a halogenated
20 hydrocarbon, e.g. dichloromethane. An alternative oxidation may be suitably activating dimethyl sulfoxide using for example, oxalyl chloride, followed by addition of an alcohol, and subsequent quenching of the reaction by the addition of an amine base, such as triethylamine. Suitable conditions for this reaction may be using an appropriate solvent, for example, a halogenated
25 hydrocarbon, e.g. dichloromethane at -78°C followed by subsequent warming to room temperature.

In a further example primary amine (-NH₂) or secondary amine (-NH-) groups may be alkylated using a reductive alkylation process employing an aldehyde
30 and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH₂] groups may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

5

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

10

In a further example amine (-CH₂NH₂) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether, e.g. a cyclic ether such as tetrahydrofuran, at a temperature from -78°C to the reflux temperature.

15

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as *n*-butyl or *t*-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile. Aromatic halogen substituents may also be subjected to palladium catalysed reactions, to introduce, for example, acid, ester, cyano or amino substituents.

25

30

In another example, sulfur atoms in the compounds, for example when present in a linker group L¹ or L² may be oxidised to the corresponding sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-

chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

5 *N*-oxides of compounds of formulae (1) or (2) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

10

Salts of compounds of formulae (1) or (2) may be prepared by reaction of a compound of formulae (1) or (2) with an appropriate base or acid in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol or an aqueous solvent using
15 conventional procedures. Salts of compounds of formulae (1) or (2) may be exchanged for other salts by use of conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of
20 formulae (1) or (2) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by
25 reaction of a mixture of enantiomers of formulae (1) or (2) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

30

In another resolution process a racemate of formulae (1) or (2) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

5

The following Examples illustrate the invention. All temperatures are in °C. Where experimental detail is not given for the preparation of a reagent it is either commercially available, or it is known in the literature, for which the CAS number is quoted. The compounds are named with the aid of Beilstein
10 Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany.

¹H NMR spectra were obtained at 300MHz or 400MHz unless otherwise indicated.

15

LCMS conditions:

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionization

Column: Luna C18(2) 100x4.6mm, 5µm particle size Analytical column

20 Column Temp: Not controlled

Mobile Phase: A: Water + 0.08% formic acid

B: Acetonitrile + 0.1% formic acid

Flow rate: 2ml/min

Gradient: Time (mins): % Composition B:

25 5

6.50 95

8.00 95

8.05 5

Run time: 10.00mins

30 Typical Injection Vol: 5µl

Detector Wavelength: DAD 205-330nm

Preparative LC conditions:

Gilson 215 liquid handler setup.

35

Column: Luna C18(2) 250x21.2mm, 5µm particle size PREP column

Column Temp: Ambient

Gradient: Variable – depends on retention of sample in LCMS screen

40 Run Time: 20 mins

Flow rate: 25ml/min

Typical Injection Vol: 750µl of 25mg/ml solution
 Detector Wavelength: 210 and 254nm

Method A:

- 5 **Mobile Phase:** A: Water + 0.08% formic acid
 B: Acetonitrile + 0.1% formic acid

Method B:

Mobile phase: A: Water + 0.1% ammonia
 B: Acetonitrile + 0.1% ammonia

10

Method C:

Mobile phase A: 10mM Ammonium acetate in water (pH 5.8)
 B: 10mM Ammonium acetate in acetonitrile (pH 5.8)

- 15
- Abbreviations used:**

Boc – *tert*-Butoxycarbonyl CDCl₃ Deuterated chloroform

DCM Dichloromethane DMF *N,N*-Dimethylformamide

d₆-DMSO Deuterated dimethylsulfoxide

EtOAc Ethyl acetate MeOH Methanol

- 20 d
- ₄
- MeOH – Deuterated methanol THF Tetrahydrofuran

Intermediate 1

5-[(Methoxy-4-oxazol-5-yl-phenylamino)methyl-sulfanylmethylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

- 25 A mixture of 3-methoxy-4-oxazol-5-yl-aniline (CAS 198821-79-3) (0.95g, 5mmol) and 5-(bismethylsulfanylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.24g) in ethanol (10ml) was stirred and heated at reflux for 2 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica eluting with 50-100% ethyl acetate / hexane to yield
- 30 the title compound as a yellow solid (1.61g, 83%). TLC R_f 0.19 (50% EtOAc/hexane).

¹H-NMR 300MHz (CDCl₃) 12.9-12.8 (1H, s, br), 7.95 (1H, s), 7.85 (1H, d), 7.60 (1H, s), 7.05 (1H, dd), 6.95 (1H, d), 4.00 (3H, s), 2.35 (3H, s), 1.78 (6H, s).

Intermediate 2**5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)phenylaminomethylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

A mixture of Intermediate 1 (500mg, 1.28mmol), aniline (2ml) and mercury (II) chloride (348mg) were stirred at room temperature for 30 minutes. The mixture was diluted in dichloromethane (20ml), filtered and washed with dichloromethane (5ml). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 50% ethyl acetate / hexane to yield the title compound as a pale yellow solid (422mg, 76%). TLC R_f 0.25 (50% EtOAc/hexane).

¹H-NMR 300MHz (CDCl₃) 12.0-11.9 (2H, s, br), 7.85 (1H, s), 7.45 (1H, d), 7.40 (1H, s), 7.05 (2H, m), 6.92 (3H, m), 6.60 (1H, dd), 6.45 (1H, d), 3.78 (3H, s), 1.80 (6H, s).

Intermediate 3**5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)(pyridin-3-ylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

A mixture of Intermediate 1 (100mg, 0.26mmol), 3-aminopyridine (100mg), mercury (II) chloride (70mg), and anhydrous THF (0.5ml) were stirred at 80°C under an atmosphere of nitrogen. After 30 minutes the mixture was cooled to room temperature, diluted with dichloromethane (20ml), filtered and washed with dichloromethane (5ml). The solvent was removed *in vacuo* and the residue purified by preparative HPLC (method A) to yield the title compound as a pale yellow solid (70mg, 63%). TLC R_f 0.46 (EtOAc). MS 437 [M+H]⁺.

¹H-NMR 300MHz (d₆-DMSO) 11.5-11.4 (2H, d, br), 8.45 (1H, s), 8.2 (1H, d), 7.60 (1H, m), 7.55-7.50 (2H, m), 7.20 (1H, dd), 6.95 (1H, s), 6.90 (1H, d), 3.90 (3H, s), 1.80 (6H, s).

Intermediates 4 – 22 were prepared in a similar manner to Intermediate 3:-

Intermediate 4**5-[Amino-(3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (250mg, 0.6mmol), ammonium hydroxide (2ml), mercury (II) chloride (174mg, 0.64mmol) to give the title compound (225mg, 92%).

TLC R_f 0.24 (50% EtOAc/heptane).

¹H-NMR 300MHz (CDCl₃) 11.45 (1H, s, br), 9.65 (1H, s, br), 7.92 (1H, s), 7.88-7.86 (1H, d), 7.60 (1H, s), 7.03-6.98 (1H, dd), 6.86 (1H, s), 5.68 (1H, s, br), 4.00 (3H, s), 1.74 (6H, s).

5 **Intermediate 5**

4-[(2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)(3-methoxy-4-oxazol-5-yl-phenylamino)methyl]piperazine-1-carboxylic acid tert-butyl ester.

From Intermediate 1 (440mg, 1.12mmol), *tert*-butyl piperazine carboxylate (420mg, 2.25mmol) and mercury (II) chloride (311mg, 1.12mmol) to afford the
10 title compound as a yellow solid (578mg, 98%). TLC R_f 0.35 (5% MeOH/DCM). MS 358 [M-H]⁻.

¹H-NMR 300MHz (CDCl₃) 9.84 (1H, s, br), 7.93 (1H, s), 7.80-7.75 (1H, d), 7.56 (1H, s), 6.78-6.70 (2H, m), 4.0 (3H, s), 3.53-3.45 (4H, m), 3.30-3.25 (4H, m) 1.77(6H, s), 1.40 (9H, s).

15 **Intermediate 6**

5-{3-Methoxy-4-oxazol-5-yl-phenylamino}[(pyridin-3-ylmethyl)amino]-methylene}-2,2-dimethyl[1,3]dioxane-4,6-dione.

From Intermediate 1 (250mg, 0.64mmol), 3-aminomethylpyridine (207mg, 1.92mmol) and mercury (II) chloride (174mg, 0.64mmol). Purification by
20 column chromatography on silica eluting with 10% methanol / dichloromethane afforded the title compound as an off-white solid (255mg, 89%). MS 451 [M+H]⁺.

¹H-NMR 300MHz (CDCl₃) 11.70 (1H, s), 10.60 (1H, s), 8.55 (1H, d), 8.25 (1H, s), 8.00 (1H, s), 7.80 (1H, d), 7.60 (1H, s), 7.40 (1H, d), 7.25 (1H, m), 6.90
25 (1H, d), 6.70 (1H, s), 4.20 (2H, d), 3.90 (3H, s), 1.80 (6H, s).

Intermediate 7

5-{3-Methoxy-4-oxazol-5-yl-phenylamino}[(furan-2-ylmethyl)amino]-methylene}-2,2-dimethyl[1,3]dioxane-4,6-dione.

From Intermediate 1 (250mg, 0.64mmol), fufurylamine (170μl, 1.92mmol) and
30 mercury (II) chloride (174mg, 0.64mmol). Purification by column chromatography on silica eluting with 10% methanol / dichloromethane afforded the title compound as an off-white solid (250mg, 89%). TLC R_f 0.62 (10% MeOH/DCM).

¹H-NMR 300MHz (CDCl₃) 8.10 (1H, s), 8.75 (1H, d), 8.45 (1H, s), 8.35 (1H, d), 7.95 (1H, d), 7.85 (1H, dd), 6.20 (1H, m), 6.10 (1H, d), 4.10 (2H, s), 3.90 (3H, s), 1.60 (6H, s).

Intermediate 8

5 5-[[[(1-Ethylpyrrolidin-2-ylmethyl)amino]-(3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (250mg, 0.64mmol), *N*-ethyl-2-aminomethylpyrrolidine (280μl, 1.03mmol) and mercury (II) chloride (174mg, 0.64mmol). Purification by column chromatography on silica eluting with 5% methanol /
10 dichloromethane yielded the title compound as an off-white solid (292mg, 97%). TLC R_f 0.52 (10% MeOH/DCM). MS 471 [M+H]⁺.

Intermediate 9

5-[1-(2,3-Dihydroindol-1-yl)-1-(3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

15 From Intermediate 1 (201mg, 0.51mmol), indoline (115μl, 1.03mmol) and mercury (II) chloride (139mg, 0.51mmol). The mixture was stirred at room temperature overnight. Purification by column chromatography on silica eluting with 3% methanol / dichloromethane yielded the title compound as a yellow solid (195mg, 82%). TLC R_f 0.27 (3% MeOH/DCM). MS 404 [(M+H)-
20 58]⁺.

¹H-NMR 300MHz (d₆-DMSO) 10.4 (1H, s, br), 8.20 (2H, s), 7.4 (1H, m), 7.25 (1H, m), 7.10 (1H, m), 6.80-6.50 (4H, m), 4.00-3.88 (2H, m), 3.65-3.50 (3H, m), 3.90-3.00 (2H, m), 1.65-1.30 (6H, m).

Intermediate 10

25 1-[(2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)-(3-methoxy-4-oxazol-5-yl-phenylamino)methyl]piperidine-4-carboxylic acid methyl ester

From Intermediate 1 (500mg, 1.28mmol), methyl isonipecolate (185mg, 1.28mmol) and mercury (II) chloride (350mg, 1.28mmol). Purification by column chromatography on silica eluting with 10% methanol /
30 dichloromethane yielded the title compound as an off-white solid (300mg, 48%). TLC R_f 0.23 (10% MeOH/DCM). MS 428 [(M+H)-58]⁺.

Intermediate 11**1-[(1-(2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)-(3-methoxy-4-oxazol-5-yl-phenylamino)methyl)amino]butyric acid ethyl ester**

From Intermediate 1 (500mg, 1.28mmol), ethyl 4-aminobutyrate hydrochloride (430mg, 1.28mmol), triethylamine (0.36ml) and mercury (II) chloride (350mg, 1.28mmol). Purification by column chromatography on silica eluting with 75% ethyl acetate / heptane afforded the title compound as an off-white solid (620mg, 100%). TLC R_f 0.74 (EtOAc).

Intermediate 12

10 **1-[(2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)-(3-methoxy-4-oxazol-5-yl-phenylamino)methyl]piperidine-4-carboxylic acid amide**

From Intermediate 1 (320mg, 0.82mmol), isonipecotamide (120mg, 0.94mmol) and mercury (II) chloride (260mg, 0.94mmol). Purification by column chromatography on silica eluting with 10% methanol / dichloromethane yielded the title compound as an off-white solid (225mg, 58%). TLC R_f 0.17 (10% MeOH/DCM). MS 493 [M+Na]⁺.

Intermediate 13**5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)-(4-pyrrolidin-1-yl-piperidin-1-yl)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

20 From Intermediate 1 (500mg, 1.28mmol), 4-(1-pyrrolidinyl)-piperidine (200mg, 1.28mmol) and mercury (II) chloride (350mg, 1.28mmol). Purification by column chromatography on silica eluting with 5% methanol / ethyl acetate afforded the title compound as an off-white solid (170mg, 27%). TLC R_f 0.10 (10% MeOH/EtOAc).

25 **Intermediate 14**

5-[(3,4-Dihydro-1H-isoquinolin-2-yl)-(3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

30 From Intermediate 1 (200mg, 0.50mmol), 1,2,3,4-tetrahydroisoquinoline (0.1ml, 0.8mmol) and mercury (II) chloride (140mg, 0.50mmol). The mixture was stirred at room temperature overnight. Purification by column chromatography on silica eluting with 2% methanol / dichloromethane yielded the title compound as a yellow solid (230mg, 94%).

HPLC RT 2.85 mins. MS 418 [(M+H)-58]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.20 (1H, s), 7.75-7.70 (1H, d), 7.50 (1H, s), 7.28-7.15 (4H, m), 6.95-6.85 (2H, m), 4.85 (2H, m), 3.95-3.85 (5H, m), 3.18-3.07 (2H, m), 1.60-1.30 (6H, m).

Intermediate 15

5 5-[(1,3-Dihydroisoindol-2-yl)-(3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (1g, 2.56mmol), isoindoline (0.44ml, 3.85mmol) and mercury (II) chloride (700mg, 2.56mmol). The mixture was stirred at room temperature overnight. Purification by column chromatography on silica
10 eluting with 10% methanol / dichloromethane to afforded the title compound as a yellow solid (951mg, 80%). MS 460 [M-H]⁻.

¹H-NMR 300MHz (d₆-DMSO) 10.3 (1H, s, br), 8.50 (1H, s), 7.78-7.75 (1H, d), 7.59 (1H, s), 7.50-7.40 (4H, m), 7.00-7.90 (2H, m), 5.23-5.10 (4H, m), 3.95 (3H, s), 1.65-1.35 (6H, m).

15 Intermediate 16

5-[(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl [1,3]dioxane-4,6-dione

From Intermediate 1 (1g, 2.56mmol), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.hydrogen chloride (0.88g, 3.85mmol), triethylamine
20 (0.51ml, 3.85mmol) and mercury (II) chloride (700mg, 2.56mmol). The mixture was stirred at room temperature overnight. Purification by column chromatography on silica eluting with 5% methanol / dichloromethane yielded the title compound as a yellow solid (250mg, 18%).

HPLC RT 2.65 mins. MS 477 [(M+H)-58]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.25
25 (1H, s), 7.77-7.72 (1H, d), 7.53 (1H, s), 7.97-6.75 (4H, m), 4.80-4.70 (2H, m), 3.95-3.90 (5H, m), 3.85 (3H, s), 3.80 (3H, s), 3.10-3.02 (2H, m), 1.65-1.30 (6H, m).

Intermediate 17

30 5-[(5-Bromo-2,3-dihydroindol-1-yl)-(3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (1g, 2.56mmol), 5-bromoindoline (762mg, 3.85mmol) and mercury (II) chloride (696mg, 2.56mmol). The mixture was stirred at room temperature overnight. Purification by column chromatography on silica

eluting with 2% methanol / dichloromethane afforded the title compound as a yellow solid (703mg, 51%). HPLC RT 3.47 mins. MS 482 [(M+H)⁺].

Intermediate 18

5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)-(methylphenethylamino)-

methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (500mg, 1.28mmol), *N*-methylphenylamine (0.37ml, 2.56mmol) and mercury (II) chloride (350mg, 1.28mmol). Purification by column chromatography on silica eluting with 5% methanol / dichloromethane afforded the title compound as an off-white solid (640mg, 100%).

10 TLC R_f 0.2 (EtOAc).

Intermediate 19

5-[(Benzylmethylamino)-(3-methoxy-4-oxazol-5-yl-phenylamino)-

methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (500mg, 1.28mmol), *N*-benzylmethylamine (0.33ml, 2.56mmol), and mercury (II) chloride (350mg, 1.28mmol). Purification by column chromatography on silica eluting with 10% methanol / dichloromethane afforded the title compound as an off-white solid (540mg, 91%). TLC R_f 0.24 (10% MeOH/DCM).

Intermediate 20

5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)-(4-phenylpiperidin-1-yl)-

methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (1.01g, 2.59mmol), 4-phenyl piperidine (0.417g, 2.59mmol), and mercury (II) chloride (703mg, 2.59mmol). Purification by column chromatography on silica eluting with 10% methanol / dichloromethane yielded the title compound as a tan solid (693mg, 53%).

25 HPLC RT 3.21 mins. MS 504 [M+H]⁺.

Intermediate 21

5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)-(2-methyl-2,3-dihydroindol-1-

yl)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

30 From Intermediate 1 (1g, 2.56mmol), 2-methylindoline (0.5ml, 3.85mmol), and mercury (II) chloride (700mg, 2.56mmol). The reaction mixture was stirred at room temperature overnight. Purification by column chromatography on silica eluting with 5% methanol / dichloromethane yielded a brown solid (1.28g).

This was recrystallised from 5% methanol / dichloromethane to give the title compound as a beige solid (1g, 82%).

HPLC RT 3.30 mins. MS 418 [(M+H)-58]⁺.

Intermediate 22

5 **5-[1-(3-Methoxy-4-oxazol-5-yl-phenylamino)-1-morpholin-4-yl-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

A mixture of Intermediate 1 (149mg, 0.38mmol), morpholine (5ml) and mercury (II) chloride (104mg, 0.38mmol) were stirred at room temperature for 18hrs. The solvent was removed *in vacuo* and the residue purified by column
10 chromatography on silica eluting 0-5% methanol / dichloromethane to yield the title compound as a yellow solid (31mg, 19%). TLC R_f 0.32 (5% MeOH/DCM). MS 430 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO) 10.0 (1H, s, br), 8.25 (1H, s), 7.48 (1H, d), 7.30 (1H, s), 6.65-6.60 (2H, m), 3.73 (3H, m), 3.60 (4H, m), 3.40-3.30 (4H, m), 3.78 (3H, s), 1.25-1.35 (6H, s).

15 **Intermediate 23**

5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)[tetrahydropyran-2-ylmethyl]-amino]methylene)-2,2-dimethyl[1,3]dioxane-4,6-dione

A mixture of Intermediate 1 (376mg, 0.965mmol) and 2-aminomethyltetrahydropyran (11mg, 0.965mmol) in tetrahydrofuran (10ml)
20 were stirred at room temperature for 18hrs. The solvent was removed *in vacuo* to yield the title compound as an off-white solid (440mg, 100%).
HPLC RT 3.63 mins. MS 400 [(M+H)-58]⁺.

Intermediates 24 - 40 were prepared in a similar manner to Intermediate 23:-
25

Intermediate 24

5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)[tetrahydrofuran-2-ylmethyl]-amino]methylene)-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (334mg, 0.856mmol), and tetrahydrofurfurylamine (0.088ml, 0.856mmol). The solvent was removed *in vacuo* to yield the title compound as a yellow solid (380mg, 100%). HPLC RT 3.34 mins. MS 444
30 [M+H]⁺.

Intermediate 25**5-[1-((S)-2-Methoxy-1-methylethylamino)-1-(3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (500mg, 1.28mmol), and (S)-(+)-1-methoxy-propylamine (230mg, 2.56mmol). The solvent was removed *in vacuo* to yield the title compound as a yellow solid (540mg, 98%). TLC R_f 0.54 (75% EtOAc/Hexane).

Intermediate 26

10 **5-[1-(3-Methoxy-4-oxazol-5-yl-phenylamino)-1-(2-methylpyrrolidin-1-yl)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (500mg, 1.28mmol), and 2-methylpyrrolidine (0.26ml, 2.56mmol). The solvent was removed *in vacuo* to yield the title compound as a yellow solid (540mg, 100%). TLC R_f 0.43 (10% MeOH/DCM).

Intermediate 27

15 **5-[[(3-Methoxy-4-oxazol-5-yl-phenylamino)(3-nitrobenzylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (1.03g, 2.64mmol), 3-nitrobenzylamine hydrochloride (498mg, 2.64mmol) and triethylamine (0.37ml, 2.64mmol). The reaction mixture was washed with water (2 X 20ml), dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to yield the title compound as a yellow gum (1.3g, 100%). HPLC RT 3.58 mins. MS 495 [M+H]⁺.

Intermediate 28

25 **4-[[[(2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)-(3-methoxy-4-oxazol-5-yl-phenylamino)methyl]amino)methyl]amino)methyl]benzonitrile**

From Intermediate 1 (1.03g, 2.64mmol), 4-cyanobenzylamine hydrochloride (446mg, 2.64mmol) and triethylamine (0.37ml, 2.64mmol). The reaction mixture was washed with water (2 X 20ml), dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to yield the title compound as a yellow gum (1.3g, 100%). HPLC RT 3.49 mins. MS 475 [M+H]⁺.

30 **Intermediate 29**

5-[(2-Imidazol-1-yl-ethylamino)-(3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (500mg, 1.28mmol), N-aminoethylimidazole (350mg, 1.92mmol) and triethylamine (0.54ml, 3.84mmol). The reaction mixture was

heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 5% methanol / dichloromethane to yield the title compound as an off white solid (370mg, 64%). TLC R_f 0.40 (10% MeOH/DCM).

5 **Intermediate 30**

3-(((2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)-(3-methoxy-4-oxazol-5-yl-phenylamino)methyl)amino)methyl)benzoic acid methyl ester

From Intermediate 1 (723mg, 1.85mmol) and 3-aminomethyl benzoic acid methyl ester (306mg, 1.85mmol). The solvent was removed *in vacuo* to yield the title compound as a yellow foam (985mg, 100%). HPLC RT 3.70 mins. MS 506 [M+H]⁺.

Intermediate 31

5-[(2-Methoxybenzylamino)-(3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (1g, 2.56mmol) and 2-methoxybenzylamine (0.33ml, 2.56mmol). The solvent was removed *in vacuo* to yield the title compound as a yellow foam (4.2g, 100%). HPLC RT 3.92 mins. MS 422 [(M+H)-58]⁺.

Intermediate 32

20 **5-[(2-Bromobenzylamino)-(3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (1g, 2.56mmol) and 2-bromobenzylamine hydrochloride (0.57g, 2.56mmol). The reaction was stirred at room temperature for 80 hours. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (60ml) and water (20ml). The organic layer was dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo* to yield the title compound as an off-white solid (1.51g, 100%). HPLC RT 4.03 mins. MS 529 [M+H]⁺.

Intermediate 33

30 **5-[[Benzo[1,3]dioxol-5-ylmethyl)amino(3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (500mg, 1.28mmol) and 3,4-(methylene-dioxy)-benzylamine (0.32ml, 2.56mmol). The reaction mixture was heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by

column chromatography on silica eluting with 50-75% ethyl acetate / heptane to yield the title compound as a yellow solid (600mg, 95%).

TLC R_f 0.70 (5% MeOH/DCM).

Intermediate 34

5 5-[(3-Methoxy-4-oxazol-5-yl-phenylamino)](naphthalene-1-ylmethyl)-amino]methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (500mg, 1.28mmol) and 1-naphthlene-methylamine (0.38ml, 2.56mmol). The reaction was heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 50-75% ethyl acetate / heptane to yield the title compound as a yellow oil (610mg, 95%). TLC R_f 0.38 (50% EtOAc/Hexane).

Intermediate 35

15 5-[(2,4-Dichlorobenzylamino)-3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (1.05g, 2.7mmol) and 2,4-dichloro-benzylamine (0.32ml, 2.56mmol). The reaction was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* to yield the title compound as a yellow solid (1.4g, 100%). HPLC RT 4.39 mins. MS 520 [M+H]⁺.

Intermediate 36

20 5-[3-Methoxy-4-oxazol-5-yl-phenylamino](4-phenoxybenzylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (500mg, 1.28mmol) and 4-phenoxybenzylamine (0.51g, 2.56mmol). The reaction was heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 75% ethyl acetate / heptane to yield the title compound as a yellow solid (630mg, 91%). TLC R_f 0.43 (50% EtOAc/Hexane).

Intermediate 37

30 5-[[[(Biphenyl-3-ylmethyl)amino](3-methoxy-4-oxazol-5-yl-phenylamino)-(4-phenoxybenzylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione

From Intermediate 1 (900mg, 2.3mmol), and 3-phenylbenzylamine (0.5g, 2.7mmol). Purification by column chromatography on silica eluting with 50% ethyl acetate / heptane afforded the title compound as an pale yellow solid (1.2g, 100%). TLC R_f 0.26 (50% EtOAc/Heptane). MS 526 [M+H]⁺.

Intermediate 38**[3-[[[2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)-(3-methoxy-4-oxazol-5-yl-phenylamino)methyl]amino)methyl]benzyl]carbamic acid benzyl ester**

From Intermediate 1 (1.5g, 3.7mmol) and (3-aminomethyl-benzyl)-carbamic acid benzyl ester (1.0g, 3.7mmol). Purification by column chromatography on silica eluting with 50-100% ethyl acetate / heptane afforded the title compound as a pale yellow solid (825mg, 35%). TLC R_f 0.13 (50% EtOAc/Heptane). MS 635 $[M+Na]^+$.

Intermediate 39

10 **5-[[[(Benzofuran-2-ylmethyl)amino]-3-methoxy-4-oxazol-5-yl-phenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

From Intermediate 1 (780mg, 2mmol) and 2-aminomethyl-benzofuran (CAS 37798-05-3) (645mg, 2mmol). Purification by column chromatography on silica eluting with 50% ethyl acetate / heptane afforded the title compound as a yellow solid (734mg, 75%). TLC R_f 0.3 (50% EtOAc/Heptane). MS 490 $[M+H]^+$.

Intermediate 40**5-[[[(Cyclohexylmethyl)amino]-3-methoxy-4-oxazol-5-yl-phenylamino)-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione**

20 From Intermediate 1 (500mg, 1.28mmol) and cyclohexanemethylamine (0.33ml, 2.56mmol). Purification by column chromatography on silica eluting with 20-40% ethyl acetate / heptane afforded the title compound as a pale yellow solid (490mg, 84%). TLC R_f 0.58 (50% EtOAc/Heptane).

Intermediate 41

25 **2-Amino-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one**

Intermediate 4 (225mg, 0.63mmol) was diluted with diphenyl ether (6ml) and heated to reflux for 10 minutes. The reaction mixture was diluted with hexane and the precipitate formed collected by filtration. The solid was dissolved in methanol and filtered, the solvent removed *in vacuo* and the resulting solid dried in a vacuum oven overnight to yield the title compound (130mg, 81%).

30 TLC R_f 0.11 (10% MeOH/DCM). MS 258 $[M+H]^+$.

1H -NMR 300MHz (d_4 -MeOH) 8.64 (1H, s), 8.40 (1H, s), 7.62 (1H, s), 7.06 (1H, s), 5.72 (1H, s), 4.20 (2H, s), 3.42 (3H, m).

Example 1**7-Methoxy-6-oxazol-5-yl-2-phenylamino-1H-quinolin-4-one**

A mixture of Intermediate 2 (408mg, 0.94mmol) in diphenylether (5ml) was stirred and heated at reflux for 30 minutes. The reaction was allowed to cool to room temperature and the resultant solid was purified by column chromatography on silica eluting with 10% methanol / dichloromethane to yield the title compound (71mg, 24%). TLC R_f 0.29 (10% MeOH/DCM). MS 334 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.50 (1H, s), 8.28 (1H, s), 7.55 (1H, s) 7.45 (2H, m), 7.30 (2H, m), 7.25 (1H, m), 7.10 (1H, s), 5.82 (1H, s), 4.95-4.75 (1H, s, br), 4.70-4.55 (1H, s, br), 4.05 (3H, s).

The compounds of Examples 2 - 15 were prepared in a similar manner to the compound of Example 1:-

Example 2**7-Methoxy-6-oxazol-5-yl-2-(pyridin-3-ylamino)-1H-quinolin-4-one**

From Intermediate 3 (48mg, 0.01mmol). Purification by column chromatography on silica eluting with 5% methanol/dichloromethane yielded the title compound (2mg, 5%). TLC R_f 0.29 (5% MeOH/DCM). MS 335 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.50 (1H, m), 8.40 (1H, s), 8.20 (1H, m) 8.15 (1H, s), 7.78-7.88 (1H, m), 7.43 (1H, s), 7.35 (1H, m), 7.02 (1H, s), 5.80 (1H, s, br), 3.98 (3H, s).

Example 3**7-Methoxy-2-morpholin-4-yl-6-oxazol-5-yl-1H-quinolin-4-one**

From Intermediate 22 (143mg, 0.33mmol). Purification by column chromatography on silica eluting with 0-10% methanol / dichloromethane yielded the title compound as an off-white solid (13mg, 12%). TLC R_f 0.09 (5% MeOH/ DCM). MS 328 [M+H]⁺. ¹H-NMR 400MHz (d₆-DMSO) mixture of 1H and 4H tautomers 11.15 (1H, s, br), 10.73 (1H, s, br), 8.42 (2H, s) 8.25-8.18 (2H, d), 7.53 (2H, s), 7.15 (1H, s), 7.02 (1H, s), 6.30 (1H, s), 5.40 (1H, s), 4.0 (6H, s), 3.80-3.55 (16H, m).

Example 4**7-Methoxy-6-oxazol-5-yl-2-[(pyridin-3-ylmethyl)amino]1H-quinolin-4-one**

From Intermediate 6 (255mg, 0.57mmol). Purification by column chromatography on silica eluting with 20% methanol / dichloromethane
5 afforded the title compound as an off-white solid (10mg, 5.3%). MS 349 [M+H]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.60 (1H, s), 8.45 (1H, d), 8.40 (1H, s), 8.25 (1H, s), 7.90 (1H, d), 7.50 (1H, s), 7.40-7.50 (1H, m), 6.95 (1H, s), 5.50 (1H, s), 4.65 (2H, s), 4.05 (3H, s).

Example 5**7-Methoxy-6-oxazol-5-yl-2-[(furan-2-ylmethyl)amino]1H-quinolin-4-one**

From Intermediate 7 (250mg, 0.57mmol). Purification by column chromatography on silica eluting with 10% methanol / dichloromethane
10 afforded the title compound as an off-white solid (17mg, 8.7%). MS 338 [M+H]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.60 (1H, s), 8.35 (1H, s), 7.50 (1H, s), 7.45 (1H, s), 7.10 (1H, s), 6.45 (2H, s), 5.80 (1H, s), 4.60 (2H, s), 4.25 (3H, s).
15

Example 6**4-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-yl)piperazine-1-carboxylic acid tert-butyl ester**

From Intermediate 5 (100mg, 0.189mmol). The reaction mixture was diluted
20 with hexane and the precipitate collected by filtration. Purification by column chromatography on silica eluting with 10% methanol / dichloromethane afforded the title compound (120mg, 33%). TLC R_f 0.21 (10% MeOH/DCM). MS 427 [M+H]⁺.

¹H-NMR 300MHz (d₄-MeOH) 8.56 (1H, s), 8.33 (1H, s), 8.31 (1H, s), 7.61 (1H, s), 7.23 (1H, s), 5.82 (1H, s), 4.15 (3H, s), 3.72-3.65 (4H, m), 3.60-3.52 (4H, m), 1.58 (9H, s).
25

Example 7**2-[(1-Ethylpyrrolidin-2-ylmethyl)amino]-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one; formate salt**

30 From Intermediate 8 (290mg, 0.62mmol). The reaction mixture was diluted with hexane, and the precipitate collected by filtration. Purification by preparative HPLC (Method A) afforded the title compound as an off-white solid (6.4mg, 3%). HPLC RT 1.24 mins. MS 369 [M+H]⁺.

Example 8**2-(2,3-Dihydroindol-1-yl)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one**

From Intermediate 9 (187mg, 0.41mmol). Purification by column chromatography on silica eluting with 5-10% methanol / dichloromethane yielded the title compound as a pale green solid (83mg, 57%). TLC R_f 0.11 (5% MeOH/DCM). MS 360 [M+H]⁺. ¹H-NMR 400MHz (d₆-DMSO) 11.50 (1H, s), 8.86-8.82 (1H, d), 8.63 (1H, s), 8.43 (1H, s), 7.72 (1H, s), 7.44-7.32 (3H, m), 7.10-7.00 (1H, m), 6.56 (1H, s), 4.30-4.18 (5H, m), 3.40-3.31 (2H, m).

Example 9

10 **1-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-yl)piperidine-4-carboxylic acid methyl ester**

From Intermediate 10 (300mg, 0.61mmol). The reaction mixture was heated at 200°C for 2 hours. Purification by column chromatography on silica eluting with 0-10% methanol / dichloromethane afforded the title compound as an off-white solid (185mg, 78%). TLC R_f 0.25 (10% MeOH/DCM). HPLC RT 1.91 mins. MS 384 [M+H]⁺.

Example 10

20 **7-Methoxy-6-oxazol-5-yl-2-[(tetrahydropyran-2-ylmethyl)amino]-1H-quinolin-4-one; formate salt**

From Intermediate 23 (441mg, 0.965mmol). The reaction mixture was heated at 220°C for 4 hours. Purification by preparative HPLC (method A) afforded the title compound as an off-white solid (36mg, 11%). HPLC RT 1.95 mins. MS 356 [M+H]⁺.

Example 11

25 **7-Methoxy-6-oxazol-5-yl-2-[(tetrahydrofuran-2-ylmethyl)amino]-1H-quinolin-4-one**

From Intermediate 24 (379mg, 0.856mmol). The reaction mixture was heated at 220°C for 4 hours. Purification by preparative HPLC (method A) afforded the title compound as an off-white solid (38mg, 13%). HPLC RT 1.75 mins. MS 342 [M+H]⁺.

Example 12

30 **7-Methoxy-6-oxazol-5-yl-2-(2-oxopyrrolidin-1-yl)-1H-quinolin-4-one**

From Intermediate 11 (600mg, 0.61mmol). The reaction mixture was heated at 190°C for 90 minutes. Purification by column chromatography on silica

eluting with 0-10% methanol / dichloromethane followed by trituration with dichloromethane afforded the title compound as an off-white solid (37mg, 9%). TLC R_f 0.38 (10% MeOH/DCM). HPLC RT 2.04 mins. MS 326 [M+H]⁺.

Example 13

5 7-Methoxy-2-((S)-2-methoxy-1-methylethylamino)-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 25 (600mg, 0.61mmol). The reaction mixture was heated at 200°C for 6 hours. Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane followed by trituration with diethyl ether afforded the title compound as an off white solid (42mg, 11%). TLC R_f 0.09 (10% MeOH/DCM). HPLC RT 1.79 mins. MS 330 [M+H]⁺.

Example 14

15 7-Methoxy-2-(2-methylpyrrolidin-1-yl)-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 26 (540mg, 1.26mmol). The reaction mixture was heated at 200°C for one hour. Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane followed by trituration with dichloromethane / diethyl ether afforded the title compound as an off-white solid (190mg, 46%). TLC R_f 0.26 (10% MeOH/DCM). HPLC RT 1.85 mins. MS 326 [M+H]⁺.

20 Example 15

1-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-yl)piperidine-4-carboxylic acid amide

From Intermediate 12 (900mg, 1.91mmol). The reaction mixture was heated at 200°C for one hour. The reaction was diluted with heptane (100ml) and the solid obtained by filtration. Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane afforded the title compound as an off-white solid (105mg, 15%). TLC R_f 0.17 (10% MeOH/DCM). HPLC RT 1.59 mins. MS 369 [M+H]⁺.

Example 16

30 7-Methoxyoxazol-5-yl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-1H-quinolin-4-one

A solution of Intermediate 13 (170mg, 0.34mmol) in diphenyl ether / N-methylpyrrolidinone (20ml / 2ml) was heated at 250°C in a microwave reactor

for 20mins. The reaction was diluted with heptane and the solid filtered off. The solid was recrystallised from methanol / dichloromethane / heptane to afford the title compound as an off-white solid (75mg, 56%). TLC R_f 0.05 (20% MeOH/DCM). HPLC RT 1.26mins. MS 395 [M+H]⁺.

5

The compounds of Examples 17 - 38 were prepared in a similar manner to the compound of Example 16:-

Example 17

10 7-Methoxy-2-(3-nitrobenzylamino)-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 27 (1.3g, 2.64mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane afforded the title compound as a brown solid (539mg, 52%). TLC R_f 0.15 (10% MeOH/DCM). MS 392 [M+H]⁺.

15 Example 18

2-(Dihydro-1H-isoquinolin-2-yl)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 14 (147mg, 0.31mmol). The mixture was diluted with hexane (100ml) and filtered. The resulting solid was purified by column chromatography on silica eluting with 8% methanol/dichloromethane to afford the title compound as a brown solid (26mg, 23%). HPLC RT 2.17 mins. MS 374 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.50 (1H, s), 8.25 (1H, s), 7.54 (1H, s), 7.29-7.22 (5H, m), 5.81 (1H, s), 4.66 (2H, s), 4.10 (3H, s), 3.80-3.73 (2H, m), 3.10-3.03 (2H, m).

25 Example 19

4-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-ylamino-methyl)benzonitrile

From Intermediate 28 (1.2g, 2.65mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane afforded the title compound as a light brown solid (502mg, 51%). TLC R_f 0.18 (10% MeOH/ DCM). MS 373 [M+H]⁺.

Example 20

2-(2-Imidazol-1-yl-ethylamino)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one; formate salt

From Intermediate 29 (0.35g, 0.77mmol). The mixture was diluted with hexane and the resulting brown solid filtered off. Purification by preparative HPLC (method A) afforded the title compound as pale brown solid (90mg, 33%). HPLC RT 1.21 mins. MS 352 [M+H]⁺.

5 **Example 21**

4-[7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-methyl]benzoic acid methyl ester

From Intermediate 30 (985mg, 1.94mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane
10 afforded the title compound as a tan solid (269mg, 34%). HPLC RT 2.08 mins. MS 406 [M+H]⁺.

Example 22

7-Methoxy-2-(2-methoxybenzylamino)-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 31 (1.42g, 3.0mmol). Purification by column
15 chromatography on silica eluting with 10-20% methanol / dichloromethane followed trituration in methanol / dichloromethane / heptane and washing with methanol afforded the title compound as a yellow solid (39mg, 12%).
TLC R_f 0.40 (10% MeOH/ DCM). MS 378 [M+H]⁺.

Example 23

20 **2-(1,3-Dihydroisoindol-2-yl)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one**

From Intermediate 15 (950mg, 2.06mmol). Purification by column chromatography on silica eluting with 10-20% methanol / dichloromethane yielded a brown solid. This was recrystallised from 5% methanol / dichloromethane to give the title compound as a beige solid (38mg, 5%).
25 HPLC RT 2.07 mins. MS 360 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.45 (1H, s) 8.00 (1H, s), 7.43 (1H, s), 7.34 (4H, s), 7.17 (1H, s), 5.53 (1H, s), 4.80-4.70 (4H, s), 4.10 (3H, s).

Example 24

2-(2-Bromobenzylamino)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

30 From Intermediate 32 (990mg, 1.88mmol). Purification by column chromatography on silica eluting with 0-10% methanol / dichloromethane afforded the title compound as an off-white solid (216mg, 27%). HPLC RT 2.18 mins. MS 427 [M+H]⁺.

Example 25**2-[(Benzo[1,3]dioxol-5-ylmethyl)amino]-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one; formate salt**

From Intermediate 33 (0.6g, 1.22mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane gave a green-brown solid. Preparative HPLC (method A) afforded the title compound as an off-white solid (44mg, 9%). TLC R_f 0.13 (10% MeOH/ DCM). MS 392 [M+H]⁺.

Example 26**2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one**

From Intermediate 16 (250mg, 0.47mmol). Purification by column chromatography on silica eluting with 5-10% methanol / dichloromethane yielded a brown solid. This was recrystallised from 5% methanol / dichloromethane to give the title compound as a beige solid (54mg, 27%). HPLC RT 2.10 mins. MS 434 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.45 (1H, s) 8.27 (1H, s), 7.53 (1H, s), 7.22 (1H, s), 6.82 (2H, m), 4.53 (2H, s), 4.08 (3H, s), 3.81 (6H, s), 3.72-3.67 (2H, m), 3.00-2.93 (2H, m).

Example 27**2-(5-Bromo-2,3-dihydroindol-1-yl)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one**

From Intermediate 17 (990mg, 2.1mmol). Purification by column chromatography on silica eluting with 5% methanol / dichloromethane gave the title compound as a brown solid (128mg, 23%). HPLC RT 2.46 mins. MS 374 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.52 (1H, s) 8.28 (1H, s), 7.55 (1H, s), 7.34-7.20 (4H, m), 7.04-6.96 (1H, m), 6.15 (1H, s), 4.71-4.63 (1H, m), 4.11 (3H, s), 3.54-3.41 (1H, dd), 2.85-2.78 (1H, dd), 1.45-1.35 (3H, d).

Example 28**7-Methoxy-2-[(naphthalen-1-ylmethyl)amino]-6-oxazol-5-yl-1H-quinolin-4-one**

From Intermediate 34 (600mg, 1.2mmol). Hexane was added to the reaction mixture and the resulting solid filtered off. Purification by column chromatography on silica followed by trituration in diethyl ether afforded the

title compound as a beige solid (95mg, 20%). TLC R_f 0.29 (10% MeOH/DCM). MS 398 $[M+H]^+$.

Example 29

2-(2,4-Dichlorobenzylamino)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

5 From Intermediate 35 (1.4g, 2.7mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane afforded the title compound as a light brown solid (459mg, 41%).

TLC R_f 0.20 (10% MeOH/ DCM). MS 416 $[M+H]^+$.

Example 30

10 **7-Methoxy-6-oxazol-5-yl-2-(4-phenoxybenzylamino)-1H-quinolin-4-one**

From Intermediate 36 (600mg, 1.11mmol). Purification by column chromatography on silica eluting with 0-15% methanol / dichloromethane followed by trituration in methanol / diethyl ether afforded the title compound as a beige solid (115mg, 24%). TLC R_f 0.27 (10% MeOH/ DCM). MS 440

15 $[M+H]^+$.

Example 31

7-Methoxy-2-(methylphenethylamino)-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 31 (640mg, 1.34mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane followed by trituration in diethyl ether afforded the title compound as a beige solid (290mg, 57%). TLC R_f 0.29 (10% MeOH/ DCM). MS 376 $[M+H]^+$.

20 **Example 32**

2-[(Biphenyl-3-ylmethyl)amino]-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

25 From Intermediate 37 (1.2g, 2.3mmol). Purification by column chromatography on silica eluting with 2-10% methanol / dichloromethane followed by preparative HPLC (method A) afforded the title compound as an off-white solid (214mg, 22%). TLC R_f 0.35 (10% MeOH/DCM). MS 424 $[M+H]^+$.

30 **Example 33**

{3-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-methyl]benzyl}carbamic acid benzyl ester

From Intermediate 38 (800mg, 1.3mmol). Purification by column chromatography on silica eluting with 5-10% methanol / dichloromethane

followed by prep HPLC (method A) afforded the title compound as an off white solid (85mg, 13%). TLC R_f 0.28 (10% MeOH/DCM). MS 511 [M+H]⁺.

Example 34

2-(Benzylmethylamino)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

- 5 From Intermediate 19 (540mg, 1.17mmol). Purification by column chromatography on silica eluting with 0-15% methanol / dichloromethane followed by trituration in diethyl ether afforded the title compound as a salmon pink solid (270mg, 64%). TLC R_f 0.50 (20% MeOH/DCM). MS 362 [M+H]⁺.

Example 35

- 10 **7-Methoxy-6-oxazol-5-yl-2-(4-phenylpiperidin-1-yl)-1H-quinolin-4-one**

From Intermediate 20 (693mg, 1.38mmol). Purification by column chromatography on silica eluting with 0-10% methanol / dichloromethane afforded the title compound as a brown solid (154mg, 28%). HPLC RT 2.42mins. MS 402 [M+H]⁺.

- 15 **Example 36**

2-[(Benzofuran-2-ylmethyl)amino]-7-methoxy-6-oxazol-5-yl-quinolin-4-one

From Intermediate 39 (734mg, 1.5mmol). Purification by column chromatography on silica eluting with 0-20% methanol / dichloromethane afforded the title compound as a brown solid (228mg, 39%).

- 20 TLC R_f 0.20 (10% MeOH/ DCM). MS 388 [M+H]⁺.

Example 37

7-Methoxy-2-(2-methyl-2,3-dihydroindol-1-yl)-6-oxazol-5-yl-1H-quinolin-4-one

- 25 From Intermediate 21 (700mg, 1.3mmol). Purification by column chromatography on silica eluting with 10% methanol/dichloromethane afforded the title compound as a brown solid (128mg, 23%). HPLC RT 2.91 mins. MS 438 [M+H]⁺. ¹H-NMR 400MHz (d₄-MeOH) 8.50 (1H, s) 8.19 (1H, s), 7.74 (1H, s), 7.51 (1H, s), 7.36-7.30 (2H, m), 7.16 (1H, s), 6.10 (1H, s), 4.18-4.08 (5H, m), 3.22-3.15 (2H, m).

- 30 **Example 38**

2-(Cyclohexylmethylamino)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

From Intermediate 40 (490mg, 1.07mmol). Purification by column chromatography eluting with 0-20% methanol / dichloromethane followed by

trituration in dichloromethane / diethyl ether afforded the title compound as a pink solid (130mg, 34%). TLC Rf 0.28 (10% MeOH/ DCM). MS 354 [M+H]⁺.

Example 39

7-Methoxy-6-oxazol-5-yl-2-piperazin-1-yl-1H-quinolin-4-one;

5 dihydrochloride

The compound of Example 6 (90mg, 2.11mmol) was dissolved in methanol (20ml) with stirring. 1.0M Hydrochloric acid (10ml) was added and the reaction stirred at room temperature for 2 hours. Mixture was concentrated *in vacuo* to give the title compound (91mg). MS 327 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO) 8.68 (1H, s), 8.42 (1H, s), 8.11 (1H, m), 7.83 (1H, s), 6.66 (1H, s),
10 4.25 (3H, s), 4.25-4.22 (4H, m), 3.50-3.45 (4H, m).

Example 40

2-(4-Acetyl-piperazin-1-yl)-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one

A solution of Example 39 (20mg, 0.05mmol) and triethylamine (0.03ml) in
15 dichloromethane (2ml) was treated with acetyl chloride (0.01ml). The mixture was stirred overnight and then washed with saturated aqueous sodium hydrogen carbonate (5ml) and saturated sodium chloride (5ml). The organic layer was dried over magnesium sulphate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by preparative HPLC
20 (method A) to give the title compound (5mg). MS 368 [M+H]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.37 (1H, s), 8.18 (1H, s), 7.43 (1H, s), 7.01 (1H, s), 5.65 (1H, s), 3.95 (3H, s), 3.60-3.75 (4H, m), 3.40-3.55 (4H, m), 2.07 (3H, s).

Example 41

3-[4-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-yl)piperazin-1-yl]propanoic acid methyl ester; formate salt

A mixture of Example 39 (10mg, 0.025mmol), triethylamine (0.007ml) and methyl acrylate (0.5ml) was stirred at 50°C for 2 hours. The mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (method A) to give the title compound (5mg). MS 413 [M+H]⁺. ¹H-NMR 300MHz (d₄-
30 MeOH) 8.52 (1H, s), 8.35 (1H, s), 8.25 (1H, s), 7.55 (1H, s), 7.15(1H, s), 5.80 (1H, s), 4.15 (3H, s), 3.75 (3H, s), 3.45-3.60 (4H, m), 2.50-2.85 (8H, m).

Example 42**2-[4-(2,2-Dimethylpropyl)piperazin-1-yl]-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one; formate salt**

A mixture of Example 39 (15mg, 0.037mmol), triethylamine (0.15ml),
5 trimethylacetaldehyde (0.06ml) and 4Å molecular sieves in THF (10ml) was
stirred at room temperature for one hour. The mixture was then treated with
sodium cyanoborohydride (16mg) and stirred for a further 3 days. The reaction
was partitioned between dichloromethane (10ml) and saturated aqueous
sodium hydrogen carbonate (10ml). The organic layer was dried, filtered and
10 the filtrate concentrated *in vacuo*. The residue was purified by preparative
HPLC (method A) to give the title compound (3mg). MS 396 [M+H]⁺. ¹H-NMR
300MHz (d₄-MeOH) 8.45 (1H, s), 8.40 (1H, s), 8.25 (1H, s), 7.55 (1H, s),
7.15(1H, s), 5.75 (1H, s), 4.05 (3H, s), 3.45-3.55 (4H, m), 2.60-2.8 (4H, m) 2.20
(2H, s), 0.95 (9H, s),

15

The compound of Example 43 was prepared in a similar manner to the
compound of Example 42:-

Example 43

20 **7-Methoxy-6-oxazol-5-yl-2-(4-pyridin-3-ylmethyl)piperazin-1-yl)-1H-quinolin-4-one; formate salt**

From Example 39 (15mg, 0.037mmol), and pyridine-3-carboxaldehyde
(0.055ml). Purification by preparative HPLC (method A) afforded the title
compound (3mg). MS 396 [M+H]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.50 (1H, s),
25 8.45 (1H, s), 8.20 (1H, s), 8.0(1H, s), 7.70-7.8(1H, d), 7.50 (1H, s), 7.25-
7.35(1H, d), 6.95 (1H, s), 5.65 (1H, s), 4.00 (3H, s), 3.60 (2H, s), 3.45-3.55
(4H, m), 2.50-2.65 (4H, m).

Example 44**2-Azetidin-1-yl-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one**

30 A mixture of Intermediate 1 (200mg, 0.5mmol), azetidine (0.12g, 1mmol), THF
(10ml) and mercury (II) chloride (140mg, 0.5mmol) were heated to 50°C for 2
hours. The solvent was removed *in vacuo* and the residue purified by column
chromatography on silica, eluting with 10% methanol/dichloromethane to yield

an off-white solid. The solid was treated with diphenyl ether (3ml) and heated to reflux for 30 minutes. The reaction mixture was diluted with hexane and the precipitate formed collected by filtration. Purification by column chromatography on silica eluting with 10% methanol/dichloromethane afforded the title compound as an off-white solid (20mg, 13%). TLC R_f 0.24 (5% MeOH/DCM). MS 298 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO) 8.20 (1H, s), 8.05 (1H, s), 7.30 (1H, s), 6.85 (1H, s), 5.0 (1H, s), 3.65-3.85 (7H, m), 2.05-2.20 (2H, m).

- 10 The compounds of Examples 45 - 48 were prepared in a similar manner to the compound of Example 44:-

Example 45

7-Methoxy-6-oxazol-5-yl-2-piperidin-1-yl-1H-quinolin-4-one.

- 15 From Intermediate 1 (200mg, 0.5mmol) and piperidine (0.17g, 1mmol). Purification by column chromatography on silica eluting with 10% methanol / dichloromethane afforded the title compound as an off-white solid (79mg, 49%). TLC R_f 0.39 (5% MeOH/DCM). MS 326 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO) 8.30 (1H, s), 8.05 (1H, s), 7.35 (1H, s), 7.00 (1H, s), 5.25 (1H, s), 3.85 (3H, s), 3.10-3.25 (4H, m), 1.35-1.55 (6H, m).

Example 46

7-Methoxy-2-((S)-2-methoxymethylpyrrolidin-1-yl)-6-oxazol-5-yl-1H-quinolin-4-one

- 25 From Intermediate 1 (200mg, 0.5mmol) and (S)-(+)-2-methoxymethylpyrrolidine (65μl, 1mmol). Purification by column chromatography on silica eluting with 5-10% methanol / dichloromethane afforded the title compound (114mg). TLC R_f 0.49 10%MeOH/DCM. MS 356 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO, 130°C) 8.25 (1H, s), 8.30 (1H, s), 7.40 (1H, s), 7.10 (1H, s), 4.25 (1H, s, br), 4.05 (3H, s), 3.60-3.45 (4H, m), 3.35 (3H, s), 2.10-1.95 (4H, m).

Example 47**3-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-ylamino)****benzonitrile**

From Intermediate 1 (200mg, 0.5mmol) and 3-aminobenzonitrile (0.12g, 1mmol). Purification by column chromatography on silica eluting with 0-5% methanol / dichloromethane afforded the title compound as a pale orange solid (6.4mg, 19%). TLC R_f 0.25 (5% MeOH/DCM). MS 359 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO) 11.3 (1H, s, br), 9.32 (1H, s, br), 8.31 (1H, s), 8.12 (1H, s), 7.98-7.91 (1H, m), 7.41 (1H, s), 7.38-7.31 (1H, m), 7.31-7.27 (1H, m), 7.02 (1H, s), 6.17-6.12 (1H, m), 3.92 (3H, s), 3.60 (4H, m), 3.30-3.40 (4H, m), 3.78 (3H, s), 1.35-1.25 (6H, s).

Example 48**7'-Methoxy-6'-oxazol-5-yl-3,4-dihydro-2H,1'H-[1,2']biquinoliny-4'-one**

From Intermediate 1 (200mg, 0.5mmol), 1,2,3,4-tetrahydroquinoline (0.1ml, 0.8mmol) and mercury (II) chloride. The mixture was stirred at room temperature overnight. Purification by column chromatography on silica eluting with 1% methanol / dichloromethane gave the desired intermediate along with an unidentified impurity. The mixture was dissolved in diphenyl ether and heated at 250°C for approximately 30 minutes. The reaction mixture was diluted with heptane and filtered. The resulting solid was purified by column chromatography on silica eluting with 5% methanol / dichloromethane to afford the title compound as a brown solid (120mg, 63%). HPLC RT 2.32 mins. MS 374 [M+H]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.55 (1H, s), 8.25 (1H, s), 7.55 (1H, s), 7.23-7.00 (5H, m), 6.00 (1H, s), 4.08 (3H, s), 3.85-3.78 (2H, m), 2.90-2.85 (2H, m), 2.12-2.02 (2H, m).

Example 49**7-Methoxy-2-(1-methyl-1H-pyrazol-3-ylamino)-6-oxazol-5-yl-1H-quinolin-4-one**

A mixture of Intermediate 1 (300mg, 0.8mmol) and 3-amino-1-methyl pyrazole (0.1g, 1mmol) in DMF (4ml) was heated to 60°C for 1 hour and then at 100°C for a further 2 hours. Water (20ml) was added and the mixture was allowed to stand overnight. The aqueous mixture was extracted with dichloromethane (3 X 10ml) and the dichloromethane fractions washed with saturated sodium

hydrogen carbonate solution (10ml). The organic layer was dried over magnesium sulphate, filtered and the solvent was removed *in vacuo* to give a brown oil. The oil was dissolved in diphenyl ether (4ml) and heated to 195°C for 10 minutes. The reaction mixture was diluted with hexane to give an oil.

- 5 The diphenyl ether / hexane solution was decanted off and the oil dissolved in dichloromethane. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (method A) to yield the title compound as a pale yellow solid (0.5mg, 0.2%). TLC R_f 0.25 (5% MeOH/DCM). MS 359 [M+H]⁺.

Example 50

10 7-Methoxy-6-oxazol-5-yl-2-pyrrolidin-1-yl-1H-quinolin-4-one

A mixture of Intermediate 1 (200mg, 0.5mmol), pyrrolidine (70mg, 1mmol) in diphenyl ether (4ml) was heated to 50°C for 2 hours and then at 195°C for 30 minutes. The reaction mixture was diluted with hexane to give an off-white solid, which was filtered off. Purification by column chromatography on silica
15 eluting with 10% methanol / dichloromethane afforded the title compound (76mg, 48%). TLC R_f 0.37 (5% MeOH/DCM). MS 312 [M+H]⁺. ¹H-NMR 300MHz (d₆-DMSO) 8.42 (1H, s), 8.20 (1H, s), 7.45 (1H, s), 7.25 (1H, s), 5.10 (1H, s), 3.95 (3H, s), 3.25-3.45 (4H, m), 1.85-2.00 (4H, m).

Example 51

20 2-Benzylamino-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one.

To a mixture of Intermediate 1 (200mg, 0.5mmol), benzylamine (0.10g, 1mmol) in diphenyl ether (4ml) was added mercury (II) chloride (140mg, 0.5mmol). The mixture was heated to 50°C for 2 hours and then to reflux for 30 minutes. The reaction mixture was diluted with hexane and the precipitate
25 formed collected by filtration. Purification by column chromatography on silica eluting with 5% methanol/dichloromethane, followed by preparative HPLC (method A) afforded the title compound as an off-white solid (20mg, 12%). TLC R_f 0.42 (5% MeOH/DCM). MS 348 [M+H]⁺. ¹H-NMR 300MHz (d₄-MeOH) 8.52 (1H, s), 8.15 (1H, s), 7.5 (1H, s), 7.20-7.40 (5H, m), 6.90 (1H, s),
30 5.60 (1H, s), 4.45 (2H, s), 4.05 (3H, s).

Example 52

1-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-yl)piperidine-4-carboxylic acid

A solution of Example 9 (150mg) in THF (10ml), methanol (2ml) and water (2ml) was treated with lithium hydroxide monohydrate (10mg) and stirred at room temperature 16 hours. The organic solvents were removed *in vacuo* and the aqueous residue was acidified with acetic acid. All solvents were removed *in vacuo* and the residue purified by column chromatography on silica eluting with 10-20% methanol / dichloromethane to give the title compound as an off white solid (46mg, 32%). TLC R_f 0.22 (20% MeOH/DCM). HPLC RT 1.72 mins. MS 370 [M+H]⁺.

Example 53

10 1-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-ylamino)butyric acid

To a suspension of Example 12 (25mg) in methanol (5ml) and water (5ml) was added sodium hydroxide (15mg). The reaction mixture was then heated to reflux for 5 hours. The solution was acidified using 2N hydrochloric acid and the resulting mixture concentrated *in vacuo*. The resulting solid suspension was filtered off, washed with water and diethyl ether and dried in a vacuum oven to give the title compound as an off-white solid (10mg). HPLC RT 1.63 mins. MS 344 [M+H]⁺.

20 The compound of Example 54 was prepared in a similar manner to Example 53:-

Example 54

25 3-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-ylamino)-methyl]benzoic acid

From Example 21 (246mg) to give the title compound as a tan solid (224mg, 94%). HPLC RT 1.87 mins. MS 392 [M+H]⁺.

Example 55

30 N-Furan-2-ylmethyl-4-(7-methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)butyramide

Example 53 (50mg, 0.146mmol), DMF (10ml), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (34mg, 0.175mmol), 1-hydroxybenzotriazole hydrate (24mg, 0.175mmol) and furfurylamine (0.015ml, 0.175mmol) were combined under a nitrogen atmosphere at room temperature. The resulting

solution was stirred at room temperature for 5 hours. The solvents were removed *in vacuo* and the resulting residue purified by preparative HPLC (method A) to give the title compound as a cream solid (27mg, 44%). HPLC RT 1.97 mins. MS 423 [M+H]⁺.

5

Examples 56 – 63 were prepared in a similar manner to Example 55:-

Example 56

7-Methoxy-2-(4-morpholin-4-yl-4-oxo-butylamino)-6-oxazol-5-yl-1H-

10 **quinolin-4-one; formate salt**

From Example 53 (50mg, 0.146mmol) and morpholine (0.02ml, 0.219mmol). Purification by preparative HPLC (method A) to give the title compound as an off-white solid (28mg). HPLC RT 1.83 mins. MS 413 [M+H]⁺.

Example 57

15 **4-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-N-(2-morpholin-4-yl-ethyl)butyramide; formate salt**

From Example 53 (50mg, 0.146mmol) and 4-(2-aminoethyl)morpholine (0.03ml, 0.219mmol). Purification by preparative HPLC (method B) afforded the title compound as an off-white solid (14mg). HPLC RT 1.32 mins. MS
20 456 [M+H]⁺.

Example 58

4-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-N-methyl-butylamide; formate salt

From Example 53 (50mg, 0.146mmol), methylamine hydrochloride (50mg, 0.729mmol) and triethylamine (0.1ml, 0.729mmol). Purification by preparative
25 HPLC (method A) followed by trituration with hot dichloromethane / ethyl acetate twice afforded the title compound as an off white solid (4mg). HPLC RT 1.69 mins. MS 357 [M+H]⁺.

Example 59

30 **7-Methoxy-2-[3-(morpholine-4-carbonyl)benzylamino]-6-oxazol-5-yl-1H-quinolin-4-one**

From Example 54 (21mg, 0.054mmol) and morpholine (0.01ml, 0.081mmol). Purification by preparative HPLC (method B then method C) gave the title compound as an off-white solid (3mg). HPLC RT 1.86 mins. MS 461 [M+H]⁺.

Example 60**3-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-methyl]-N-methylbenzamide**

From Example 54 (21mg, 0.054mmol), methylamine hydrochloride (10mg) and triethylamine (0.1ml). Purification by preparative HPLC (method B then method C) afforded the title compound as an off-white solid (0.5mg). HPLC RT 1.80 mins. MS 405 [M+H]⁺.

Example 61

10 **4-{3-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-methyl]benzoylamino}piperidine-1-carboxylic acid tert-butyl ester**

From Example 54 (32mg), Boc-(4-amino)-piperidine hydrochloride (20mg) and triethylamine (0.1ml). Purification by preparative HPLC (method B then method C) yielded the title compound as an off-white solid (1mg). HPLC RT 2.40 mins. MS 574 [M+H]⁺.

15 **Example 62**

3-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-methyl]-N-pyridin-2-ylmethylbenzamide

From Example 54 (44mg) and 2-(aminomethyl)pyridine (0.02ml). Purification by preparative HPLC (method C) afforded the title compound as an off white solid (26mg). HPLC RT 1.69 mins. MS 482 [M+H]⁺.

Example 63**3-[(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-ylamino)-methyl]-N-(2-morpholin-4-yl-ethyl)benzamide; acetate salt**

From Example 54 (37mg) and 4-(2-aminoethyl)morpholine (0.03ml). Purification by preparative HPLC (method C) afforded the title compound as an off-white solid (28mg). HPLC RT 1.46 mins. MS 504 [M+H]⁺.

Example 64**N-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydro-quinolin-2-yl)methane sulfonamide**

30 To a stirred solution of Intermediate 41 (0.02g, 0.08mmol) in dichloromethane (5ml), was added methane sulfonyl chloride (9mg, 0.008mmol) followed by pyridine (0.1ml). After 2 hours the reaction mixture was taken up in dilute acetic acid (5ml) and extracted into dichloromethane (20ml). The organic layer was washed with saturated aqueous sodium chloride (10ml), separated,

dried over magnesium sulphate, filtered and the solvent removed *in vacuo*. The residue was washed with dichloromethane and ethyl acetate, then dried in a vacuum oven overnight, to give the title compound (5mg, 19%). TLC R_f 0.54 (10% MeOH/DCM). MS 336 [M+H]⁺. ¹H-NMR 300MHz (d₄MeOH) 8.18 (1H, s), 8.12 (1H, s), 7.54 (1H, s), 7.04 (1H, s), 6.75 (1H, s), 3.96 (3H, s), 3.38 (3H, s).

The compounds of Examples 65 - 66 were prepared in a similar manner to the compound of Example 64:-

10

Example 65

1-Ethyl-3-(7-methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-yl)urea

Intermediate 41 (20mg), ethyl isocyanate (0.2ml) DMF (5ml) and dichloromethane (5ml) were combined under a nitrogen atmosphere and heated to 84°C for 3hours. The solvents were removed *in vacuo* and the residue triturated with dichloromethane. Purification by preparative HPLC (method A) afforded the title compound as an off-white solid (4mg). HPLC RT 2.03 mins. MS 329 [M+H]⁺.

Example 66

N-(7-Methoxy-6-oxazol-5-yl-4-oxo-1,4-dihydroquinolin-2-yl)acetamide

Intermediate 41 (80mg), acetic anhydride (32mg) and DMF (5ml) were combined under a nitrogen atmosphere and heated to 90°C for 16 hours. The reaction mixture was evaporated *in vacuo* and the residue purified by preparative HPLC (method A) to give the title compound as an off-white solid (3mg). HPLC RT 1.86 mins. MS 300 [M+H]⁺.

Example 67

2-(Benzylmethylamino)-7-methoxy-6-oxazol-5-yl-1H-quinoline-4-thione

A suspension / solution of Example 34 (100mg, 0.28mmol) in dry toluene (10ml) was treated with Lawesson's reagent (134mg, 0.33mmol) and the mixture heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 0-20% methanol / dichloromethane followed by preparative HPLC (method A) to give the title compound as a yellow solid (1mg, 1%). HPLC RT 2.85 mins. MS 378 [M+H]⁺.

The ability of the compounds of the invention to inhibit the IMPDH enzymes may be determined using the following assays:

Abbreviations used:

5	IMPDH	Inosine 5'-monophosphate dehydrogenase
	IMP	Inosine 5'-monophosphate
	XMP	Xanthosine 5'-monophosphate
	NAD	β - Nicotinamide adenine dinucleotide
	NADH	β - Nicotinamide adenine dinucleotide, reduced form
10	MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

Assay Protocol 1

IMPDH catalyses the NAD dependent oxidation of IMP to XMP with concomitant reduction of the coenzyme. IMPDH activity was determined by monitoring the production of the fluorescent product, NADH. Assays were performed in a final volume of 200 μ l containing IMPDH (2 μ g), NAD (100 μ M), IMP (100 μ M), 1% DMSO, 30mM KCl and 100mM Tris/HCl, pH7.5. Fluorescence (excitation 340nm / emission 465nm) was read continuously at 25°C for 30 minutes. From this data, initial rates (i.e. change in fluorescence intensity per minute) were calculated. To determine the IC₅₀ values, test compounds were prepared at an initial concentration of 1.0mM in 100% DMSO, then diluted in assay buffer to 0.2mM. Further dilutions were made in assay buffer containing 20% DMSO, prior to diluting 20-fold into the assay; to allow testing across the range 0.3nM to 10 μ M.

The functional effect of the compounds of the invention may be demonstrated using the following assay:

PBMC Proliferation Assay

Peripheral blood mononuclear cells were isolated from freshly taken human blood using standard procedures. Cells were plated out in RPMI medium containing 5% human serum in the presence and absence of inhibitor. PHA (25 μ l of 30 μ g/ml solution to each well) was added and the plates were incubated at 37°C in an atmosphere of 95% air/5% CO₂ for 48 hours. 0.5 μ Ci

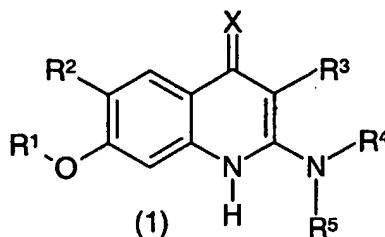
- of tritiated thymidine was added to each well and the plates were incubated for a further 18 hours. The contents of the plate were transferred to a filter plate and the cells washed with saline. The plates were dried, microscintillation fluid was added to each well and the plate was counted on a
- 5 scintillation counter. IC_{50} values were calculated by plotting inhibitor concentration versus %inhibition.

The assay described above can be carried out using anti-CD3 (40 μ l of 3750ng/ml concentration to each well) stimulation instead of PHA.

- 10 Compounds of the invention such as compounds of the Examples inhibit IMPDH enzymes with IC_{50} values of 5 μ M or below.

CLAIMS

1. A compound of formula (1):



5 wherein:

X is an O or S atom;

R¹ is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R² is a -CN group or an optionally substituted heteroaromatic group;

10 R³ is a hydrogen atom or an alkyl, -CN, -CO₂H, -CO₂R⁶ or -CONR⁷R⁸ group, in which R⁶ is an alkyl group and R⁷ and R⁸, which may be the same or different, is each a hydrogen atom or an alkyl group;

15 R⁴ is a chain -Alk¹-L¹-Alk²-R⁹ in which Alk¹ is a covalent bond or an optionally substituted aliphatic chain, L¹ is a covalent bond or a linker atom or group, Alk² is a covalent bond or a C₁₋₃ alkylene chain and R⁹ is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; provided that R⁴ is not a hydrogen atom;

R⁵ is a hydrogen atom or an alkyl group;

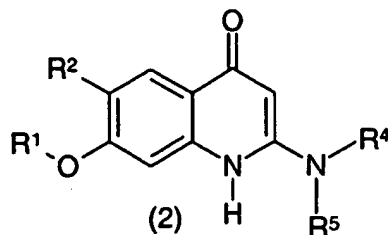
20 or NR⁴R⁵ forms an optionally substituted heterocycloaliphatic ring optionally fused to an optionally substituted monocyclic C₆₋₁₂aromatic group or an optionally substituted monocyclic C₁₋₉heteroaromatic group;

and the salts, solvates, hydrates, tautomers, isomers or *N*-oxides thereof;

provided that the compound of formula (1) is other than:

25 7-methoxy-2-methylamino-6-oxazol-5-yl-1H-quinolin-4-one or
2-dimethylamino-7-methoxy-6-oxazol-5-yl-1H-quinolin-4-one.

2. A compound according to Claim 1 which has the formula (2):



wherein R¹, R², R⁴ and R⁵ are as defined in Claim 1.

3. A compound according to Claim 1 or 2, wherein R¹ is a C₁₋₆ alkyl group.

5

4. A compound according to Claim 3, wherein R¹ is a methyl group.

5. A compound according to any one of Claims 1 to 4, wherein R² is an optionally substituted heteroaromatic group.

10

6. A compound according to Claim 5, wherein R² is a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen.

15

7. A compound according to Claim 6, wherein R² is an oxazole group.

8. A compound according to any one of Claims 1 to 7, wherein R⁴ is the chain -Alk¹-R⁹.

20

9. A compound according to Claim 8, wherein Alk¹ is a covalent bond and R⁹ is an optionally substituted phenyl or monocyclic heteroaromatic group.

25

10. A compound according to Claim 9, wherein R⁹ is an optionally substituted phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group.

11. A compound according to Claim 8 wherein Alk¹ is an optionally substituted aliphatic chain and R⁹ is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.

12.A compound according to Claim 11 wherein Alk¹ is a C₁₋₃ alkylene chain.

5 13.A compound according to Claim 11 or Claim 12 wherein R⁹ is optionally substituted azetidiny, pyrrolidiny, pyrrolidinonyl, piperidiny, imidazolidiny, thiazolidiny, piperaziny, N-C₁₋₆ alkylpiperaziny, especially N-methyl piperaziny, N-C₁₋₆ alkylpyrrolidiny, especially N-methylpyrrolidiny, N-C₁₋₆ alkylpiperidiny, especially N-methylpiperidiny,
10 homopiperaziny, morpholiny, thiomorpholiny, oxazolidiny, tetrahydrofurany, tetrahydropyrany, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆ alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidiny, pyridaziny, pyraziny, tetrazolyl or triaziny.

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14.A compound according to Claim 11 or Claim 12 wherein R⁹ is an optionally substituted C₃₋₆ cycloalkyl group.

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15.A compound according to any one of Claims 1 to 14 wherein R⁵ is a hydrogen atom or a methyl group.

16.A compound according to any one of Claims 1 to 7 wherein NR⁴R⁵ forms an optionally substituted heterocycloaliphatic group.

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17.A compound according to Claim 16 wherein NR⁴R⁵ is an optionally substituted azetidiny, pyrrolidiny, piperidiny, piperaziny, N-C₁₋₆ alkylpiperaziny, homopiperaziny, morpholiny or thiomorpholiny group.

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18.A compound according to Claim 17 wherein NR⁴R⁵ is an optionally substituted pyrrolidiny or piperidiny group.

19. A compound according to any one of Claims 16 to 18 wherein NR^4R^5 is fused to an optionally substituted phenyl or five or six membered heteroaryl group.
- 5 20. A compound according to Claim 19 in which NR^4R^5 is an optionally substituted 2,3-dihydro-1*H*-indolyl, 2,3-dihydro-1*H*-isoindolyl, 1,2,3,4-tetrahydroquinolinyl or 1,2,3,4-tetrahydroisoquinolinyl group.
21. A compound which is:
- 10 2-(2,3-Dihydroindol-1-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
2-(Dihydro-1*H*-isoquinolin-2-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
2-(1,3-Dihydroisoindol-2-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
15 2-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
2-(5-Bromo-2,3-dihydroindol-1-yl)-7-methoxy-6-oxazol-5-yl-1*H*-quinolin-4-one;
7-Methoxy-2-(2-methyl-2,3-dihydroindol-1-yl)-6-oxazol-5-yl-1*H*-quinolin-4-one;
20 7'-Methoxy-6'-oxazol-5-yl-3,4-dihydro-2*H*,1'*H*-[1,2']biquinolinyl-4'-one;
and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.
- 25 22. A pharmaceutical composition comprising a compound according to Claim 1, together with one or more pharmaceutically acceptable carriers, excipients or diluents.
23. Use of a compound of Claims 1-20, for the manufacture of a
30 medicament for the treatment of cancer, inflammatory disorders, autoimmune disorders, psoriatic disorders and viral disorders.

INTERNATIONAL SEARCH REPORT

Internat. application No

PCT/60 J2/04754

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/422 A61P43/00 C07D413/04 C07D413/14 C07D521/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

25 February 2003

Date of mailing of the international search report

05/03/2003

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/04754

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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